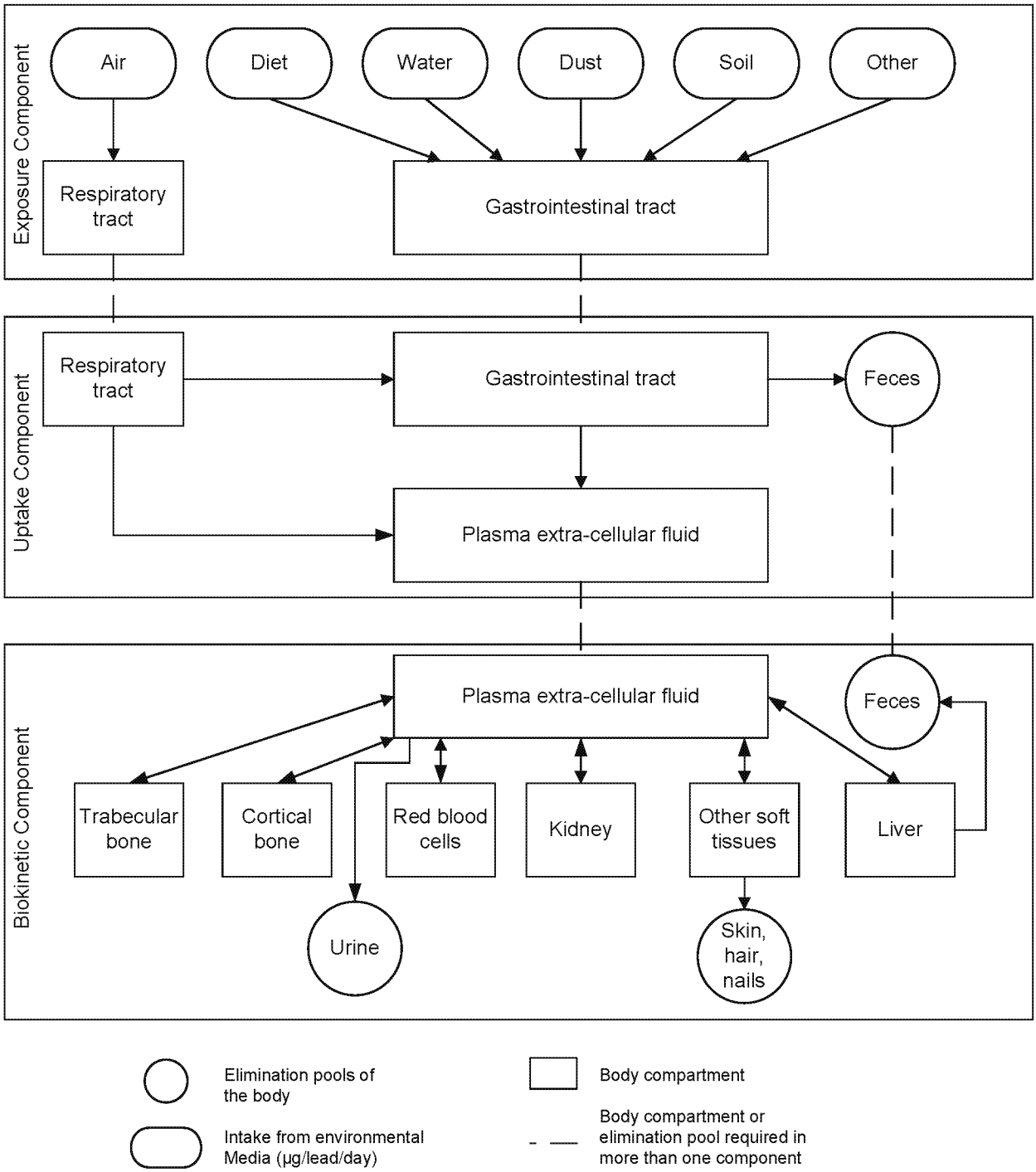
children (O'Flaherty 1995a), adults (O'Flaherty 1993), and Cynomolgus monkeys (*M. fasicularis*) (O'Flaherty et al. 1998). Model parameters were modified to correspond with available information on species- and age-specific anatomy and physiological processes described above. Comparisons of predicted and observed PbB in children and adults are reported in O'Flaherty (1993, 1995a). MacMillan et al. (2015) evaluated performance of the model for predicting population blood and bone Pb levels in a convenience sample of 263 individuals (age range 1–83 years) who experienced low chronic exposure. Based on this evaluation, model performance for predicting general trends in population PbBs and cortical bone Pb concentrations was improved by revising parameters that determine binding of Pb in red blood cells. Revisions included decreasing the maximum and affinity constants (*BIND* and *KBIND*, respectively) and increasing clearance of Pb from blood to bone by increasing the permeability constant for Pb diffusion across the canaliculi-bone interface from canaliculi to bone (P_0).

3.1.5.2 IEUBK Model

The IEUBK Model for Lead in Children simulates Pb exposure, uptake, and disposition in human children from birth to age 7 years (EPA 1994a, 1994b, 2002a; White et al. 1998). Figure 3-2 shows a conceptualized representation of the IEUBK Model. The model has four major submodels: (1) exposure model, in which average daily intakes of Pb (µg/day) are calculated for each inputted exposure concentration (or rates) of Pb in air, diet, dust, soil, and water; (2) uptake model, which converts environmental media-specific Pb intake rates calculated from the exposure model into a media-specific time-averaged uptake rate (µg/day) of Pb to the central compartment (blood plasma); (3) biokinetic model, which simulates the transfer of absorbed Pb between blood and other body tissues, elimination of Pb from the body (via urine, feces, skin, hair, and nails), and predicts an average PbB for the exposure time period of interest; and (4) blood Pb probability model, which applies a log-normal distribution (using geometric mean and geometric standard deviation for parameters) to predict probabilities for the occurrence of a specified given PbB in a population of similarly exposed children.

Exposure Model. The exposure model simulates intake of Pb (µg/day) for inputted exposures to Pb in air (µg/m^3), drinking water (µg/L), soil-derived dust (µg/g), or diet (µg/day). The exposure model operates on a 1-year time step, the smallest time interval for a single exposure event. The model accepts inputs for media intake rates (e.g., air volumes, breathing rates, drinking water consumption rate, soil and dust ingestion rate). The air exposure pathway is partitioned in exposures to outdoor air and indoor air, with age-dependent values for time spent outdoors and indoors (hours/day). Exposure to Pb to soil-derived

Figure 3-2. Structure of the IEUBK Model for Lead (Pb) in Children*



*Schematic for integrated Pb exposure-kinetics model in which simulated multi-media exposures are linked to simulations of lead uptake (i.e., absorption into the plasma-extracellular fluid), tissue distribution, and excretion).

Sources: EPA 1994a, 1994b

dust is also partitioned into outdoor and indoor contributions. The intakes from all ingested exposure media (diet, drinking water, soil-derived dust) are summed to calculate a total intake to the gastrointestinal tract, for estimating capacity-limited absorption (see description of the uptake model).

Uptake Model. The uptake model simulates Pb absorption for the gastrointestinal tract as the sum of capacity-limited (represented by a Michaelis-Menten type relationship) and unlimited processes (represented by a first-order, linear relationship). These two terms are intended to represent two different mechanisms of Pb absorption, an approach that is in accord with limited available data in humans and animals that suggest a capacity limitation to Pb absorption (see Section 3.2.1). One of the parameters for the capacity-limited absorption process (that represents that maximum rate of absorption) is age-dependent. The above representation gives rise to a decrease in the fractional absorption of ingested Pb as a function of total Pb intake as well as an age-dependence of fractional Pb absorption. Absorption fractions are also medium-specific. At 30 months of age, at low intakes (<200 μg/day), below the rates at which capacity-limitation has a significant impact on absorption, the fraction of ingested Pb in food or drinking water that is absorbed is 0.5 and decreases to approximately 0.11 (intake, >5,000 μg/day). For Pb ingested in soil or dust, fractional absorption is 0.35 at low intakes (<200 μg/day) and decreases to 0.09 (intake, >5,000 μg/day).

The uptake model assumes that 32% of inhaled Pb is absorbed. This value was originally assigned based on a scenario of exposure to active smelter emissions, which assumed the particle size distribution in the vicinity of an active Pb smelter (<1 μm, 12.5%; 1–2.5 μm, 12.5%; 2–15 μm, 20%; 15–30 μm, 40%; >30 μm, 15%); size-specific deposition fractions for the nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract; and region-specific absorption fractions. Pb deposited in the alveolar region is assumed to be completely absorbed from the respiratory tract, whereas Pb deposited in the nasopharyngeal and tracheobronchial regions (30–80% of the Pb particles in the size range 1–15 μm) is assumed to be transported to the gastrointestinal tract.

Biokinetics Model. The biokinetics model includes a central compartment, six peripheral body compartments, and three elimination pools (urine, feces, lumped pool representing skin, hair, and nails). The body compartments include plasma and extracellular fluid (central compartment), red blood cells, kidney, liver, trabecular bone, cortical bone, and other soft tissue (EPA 1994a). The model simulates growth of the body and tissues, compartment volumes, and Pb masses and concentrations in each compartment. PbB at birth (neonatal) is assumed to be 0.85 of the maternal blood Pb. Neonatal Pb masses and concentrations are assigned to other compartments based on a weighted distribution of the

neonatal PbB. Exchanges between the central compartment and tissue compartments are simulated as first-order processes, which are parameterized with unidirectional, first-order rate constants. Bone is simulated as two compartments: a relatively fast trabecular bone compartment (representing 20% of bone volume) and a relatively slow cortical bone compartment (representing 80% of the bone volume). Saturable uptake of Pb into erythrocytes is simulated, with a maximum erythrocyte Pb concentration of 12 μg/dL. Excretory routes simulated include urine, from the central compartment; bile-feces, from the liver; and a lumped excretory pathway representing losses from skin, hair and nail, from the other soft tissue compartment.

Blood Pb Probability Model. Inputs to the IEUBK Model are exposure point estimates that are intended to represent time-averaged central tendency exposures. The output of the model is a central tendency estimate of PbB for children who might experience the inputted exposures. However, within a group of similarly exposed children, PbBs would be expected to vary among children as a result of inter-individual variability in media intakes, absorption, and biokinetics. The model simulates the combined impact of these sources of variability as a lognormal distribution of PbB for which the geometric mean is given by the central tendency PbB outputted from the biokinetics model and the GSD is an input parameter. The resulting lognormal distribution also provides the basis for predicting the probability of occurrence of given PbB within a population of similarly exposed children. The model can be iterated for varying exposure concentrations (e.g., a series of increasing soil Pb concentrations) to predict the media concentration that would be associated with a probability of 0.05 for the occurrence of a PbB exceeding 10 μg/dL. A subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability and uncertainty in exposure and absorption (Goodrum et al. 1996; Griffin et al. 1999). This extension of the model provides an alternative to the blood Pb probability model for incorporating, explicitly, estimates of variability (and uncertainty in variability) in exposure and absorption into predictions of an expected probability distribution of PbBs.

Performance of the IEUBK Model has been evaluated for predicting observed PbBs in children (Hogan et al. 1998; Li et al. 2016; Von Lindern et al. 2003, 2016). The largest evaluation utilized longitudinal exposure and blood Pb data for approximately 2,200 children who resided near a former smelter in northern Idaho (Bunker Hill site) during a 14-year period of remediation activities (Von Lindern et al. 2003, 2016). The observed annual blood Pb geometric means ranged from 2.5 to 10.6 μg/dL. The model predicted the time course of the observed PbBs as the remediation progressed when the gastrointestinal absorption fraction was calibrated to agree with blood Pb observations (Von Lindern et al. 2003). A similar outcome was obtained in a subsequent analysis in which the gastrointestinal absorption fraction

was adjusted to agree with site measurements of soil Pb RBA, and soil and dust ingestion rates were calibrated to the blood Pb observations (Von Lindern et al. 2016). The mean difference between predicted and observed annual geometric mean PbBs (predicted - observed) was -0.31 μg/dL (range: -1.07, 1.93) and the mean relative percent difference was -8.4% (range: -23–21%). Applications of the IEUBK Model to the Bunker Hill site were reviewed by the National Research Council (NRC 2005). Hogan et al. (1998) evaluated the IEUBK Model performance based on residential exposure and blood data for approximately 478 children who resided near three Pb mining and smelting sites. The observed geometric means for the three sites ranged from 5.2 to 6.8 μg/dL. The IEUBK Model predictions agreed reasonably well with observations for children whose exposures were predominantly from their residence (e.g., who spent no more than 10 hours/week away from home). The mean difference between predicted and observed site geometric mean PbBs (predicted-observed) was 0.03 μg/dL (range -0.6–0.7) and the mean relative percent difference was -0.4% (range -12–10%). The predicted geometric mean PbBs were within 0.7 μg/dL of the observed geometric means at each site. The prediction of the percentage of children expected to have PbBs exceeding 10 μg/dL were within 4% of the observed percentage at each site. Li et al. (2016) compared predictions of PbB to observations in a cohort of 760 children in Central China. The observed residence area geometric means ranged from 5 to 14 μg/dL. When exposure parameters for set to the study population (e.g., exposure media Pb concentration and intakes), predicted and observed PbBs were not significantly different. The mean difference between predicted and observed geometric mean PbBs for 21 residence areas (predicted-observed) was 0.55 μg/dL (range -2.0–3.2) and the mean relative percent difference was 3.5% (range -32–28%). These evaluations provide support for the validity of the IEUBK Model for estimating PbBs in children at sites where their exposures can be adequately characterized. Similar empirical comparisons of the IEUBK Model have shown that agreement between model predictions and observed PbBs at specific locations is influenced by numerous factors, including the extent to which the exposure and blood Pb measurements are adequately matched, and site-specific factors (e.g., soil characteristics, behavior patterns, bioavailability) that may affect Pb intake or uptake in children (Bowers and Mattuck 2001; Von Lindern et al. 2003, 2016). In addition to the above empirical comparisons, the computer code used to implement the IEUBK Model (IEUBK version 0.99d) has undergone an independent validation and verification and has been shown to accurately implement the conceptual IEUBK Model (Zaragoza and Hogan 1998).

3.1.5.3 Leggett Model

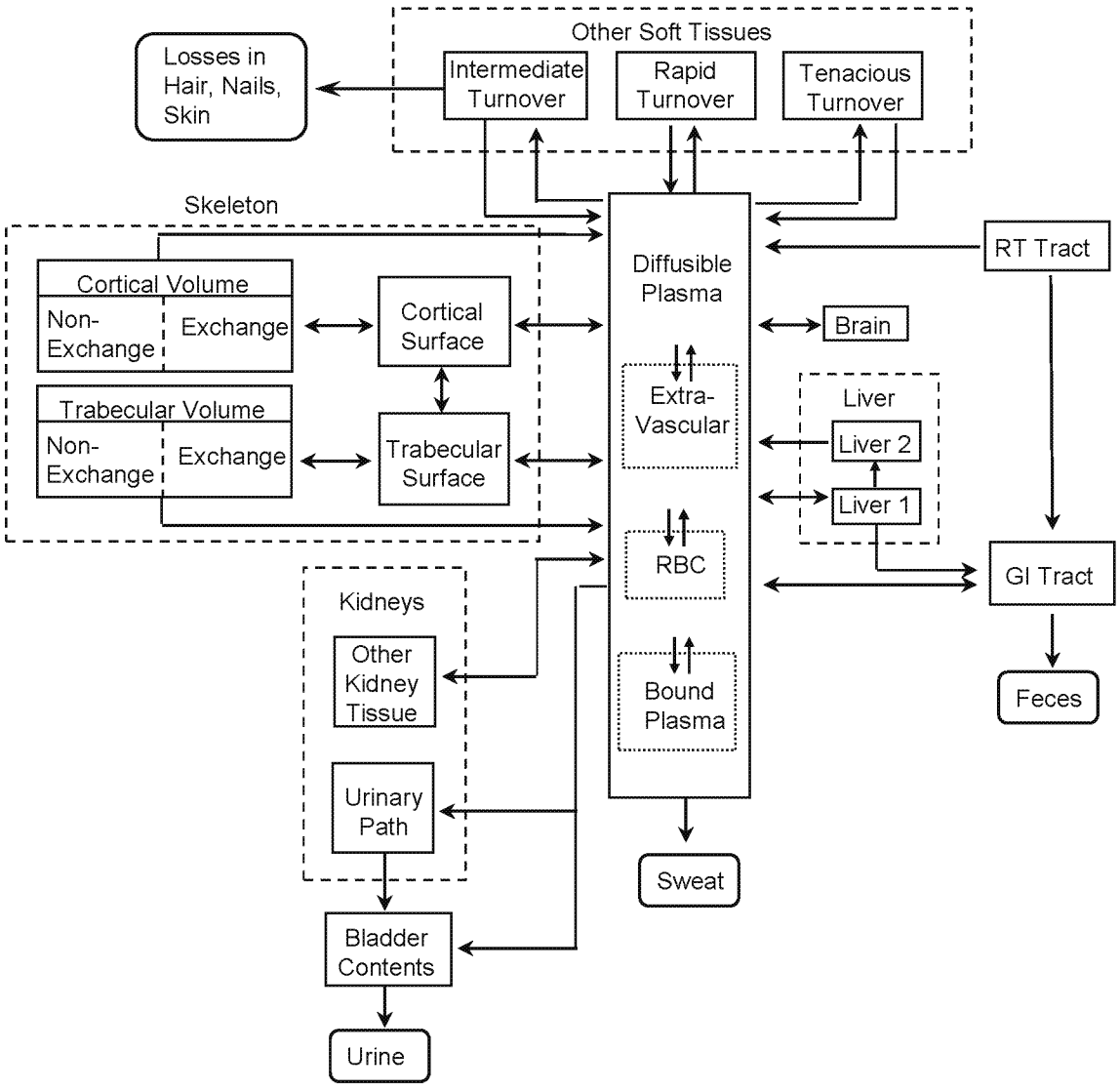
The Leggett Model simulates Pb intake, absorption, and disposition in humans, from birth through adulthood (Leggett 1993). Figure 3-3 shows a conceptualized representation of the model, including the movement of Pb from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between diffusible blood plasma, soft tissues, bone compartments, and excretion from liver, kidneys, and sweat. A detailed exposure module is not linked to the Leggett Model; rather, Pb exposure estimates are incorporated into the model as age-specific point estimates of average daily intake (μg/day) from inhalation and ingestion. A description of the model and its potential application to risk assessment are provided below.

The Leggett Model includes a central compartment, 15 peripheral body compartments, and 4 elimination pools (urine, feces, sweat, and lumped pool representing skin, hair, and nails), as illustrated in Figure 3-3. Transport of Pb from blood plasma to tissues is assumed to follow first-order kinetics. Transfer rate constants vary with age and PbB. Above a nonlinear threshold concentration in red blood cells (assumed to be 60 μg/dL), the rate constant for transfer to red blood cells declines and constants to all other tissues increase proportionally (Leggett 1993). This replicates the nonlinear relationship between plasma and red blood cells observed in humans (see Section 3.1.2). The model simulates blood volume as an age-dependent function, which allows simulation of plasma and PbBs. Pb masses are simulated in all other tissues (tissue volumes are not simulated).

Unidirectional, first-order transfer rates (day^{-1}) between compartments were developed for six age groups, and intermediate age-specific values are obtained by linear interpolation. The total transfer rate from diffusible plasma to all destinations combined is assumed to be 2,000 day^{-1}, based on isotope tracer studies in humans receiving Pb via injection or inhalation. Values for transfer rates in various tissues and tissue compartments are based on measured deposition fractions or instantaneous fractional outflows of Pb between tissue compartments (Leggett 1993).

The Leggett Model was developed from a biokinetic model originally developed for the International Commission on Radiological Protection (ICRP) for calculating radiation doses from environmentally important radionuclides, including radioisotopes of Pb (Leggett 1993). The Leggett Model simulates age-dependent bone physiology using a model structure developed for application to the alkaline earth elements, but parameterized using data specific to Pb where possible. The model simulates both rapid

Figure 3-3. Compartments and Pathways of Lead (Pb) Exchange in the Leggett Model*



*Schematic model for Pb kinetics in which Pb distribution is represented by exchanges between the central plasma-extracellular fluid and tissue compartments. Bone is represented as having surface (which rapidly exchanges with plasma-extracellular fluid) and volume compartments; the latter simulates slow exchange with the surface and slow return of Pb to the plasma-extracellular fluid from bone resorption.

GI = gastrointestinal; RBC = red blood cell; RT = respiratory

Source: Leggett 1993

exchange of Pb with plasma via bone surface and slow loss by bone resorption. Cortical bone volume (80% of bone volume) and trabecular bone volume (20% of bone volume) are simulated as bone surface compartments, which rapidly exchange Pb with the blood plasma, and bone volume, within which are *exchangeable* and *nonexchangeable* pools. Pb enters the exchangeable pool of bone volume via the bone surface and can return to the bone surface, or move to the nonexchangeable pool, from where it can return to the blood only when bone is resorbed. Rate constants for transfer of Pb from the nonexchangeable pools and blood plasma vary with age to reflect the age-dependence of bone turnover.

The liver is simulated as two compartments: one compartment has a relatively rapid uptake of Pb from plasma and a relatively short removal half-life (days) for transfers to plasma and to the small intestine by biliary secretion, and a second compartment simulates a more gradual transfer to plasma of approximately 10% of Pb uptake in liver. The kidney is simulated as two compartments: one that exchanges slowly with blood plasma and accounts for Pb accumulation in kidney tissue, and a second compartment that receives Pb from blood plasma and rapidly transfers Pb to urine, with essentially no accumulation (urinary pathway). Other soft tissues are simulated as three compartments representing rapid, intermediate, and slow turnover rates (without specific physiologic correlates). Other excretory pathways (hair, nails, and skin) are represented as a lumped pathway from the intermediate turnover rate soft tissue compartment.

The Leggett Model simulates Pb intakes from inhalation, ingestion, or intravenous injection. The latter was included to accommodate model evaluations based on intravenous injection studies in humans and animal models. The respiratory tract is simulated as four compartments into which inhaled Pb is deposited and absorbed with half-times of 1, 3, 10, and 48 hours. Four percent of the inhaled Pb is assumed to be transferred to the gastrointestinal tract. These parameter values reflect the data on which the model was based, which were derived from studies in which human subjects inhaled submicron Pb-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). These assumptions would not necessarily apply to exposures to large airborne particles (see Section 3.1.1). Absorption of ingested Pb is simulated as an age-dependent fraction of the ingestion rate, declining from 0.45 at birth to 0.3 at age 1 year (to age 15 years), and to 0.15 after age 25 years.

Output from the Leggett Model has been compared with data in children and adult subjects exposed to Pb in order to calibrate model parameters (Leggett et al. 1993; Pounds and Leggett 1998). Nie et al. (2005) evaluated performance of the Leggett Model for predicting bone Pb concentrations in 539 Pb workers. The data included periodic monitoring of PbBs and XRF bone Pb measurements made in 1994 and 1999.

Pb intakes of each individual were calibrated to agree with measured PbBs. The Leggett Model underpredicted observed cortical bone Pb concentrations by a factor of 3–4, and underpredicted trabecular bone Pb concentration by a factor of 12–18. EPA (2014a) evaluated performance of the Leggett Model for predicting PbBs in children and blood and bone Pb concentrations in adults. The evaluation of predictions for children used data on blood lead concentrations reported in the NHANES for the years 2007-2008, and required making assumptions about Pb exposures in this population. The Leggett Model overpredicted observed PbBs in children 1–7 years of age by a factor of 2–3. Cal EPA (2013) evaluated the Leggett Model for predicting PbBs in smelter workers whose occupational exposures were interrupted during a workers strike. Pre-hire background Pb intakes and pre-strike intakes were calibrated to agree with measured PbBs and the predicted rate of decline in blood Pb that occurred during the strike period was compared to observations. Cal EPA (2013) reported "the average difference between the measured and predicted post-strike BLL was unacceptably large and indicated significant under-prediction of BLLs". The average difference was >4 μg/dL in a cohort that had a mean post-strike PbB of 31 μg/dL (no further details were provided). Performance was substantially improved when various parameters were calibrated to the observations. These included parameters that control transfers between plasma and bone and red blood cell saturation (see Cal EPA [2013] for details of parameter values changes). The mean difference between predicted and observed annual geometric mean PbBs (predicted-observed) was -0.9 μg/dL (range -26–32) and the mean relative percent difference was -8.8% (range: -55–320%). Cal EPA (2013) reported several other evaluations of their recalibrated model, including observed and predicted relationships between plasma and whole PbBs in adults, and predicted distribution of Pb in bone and soft tissues compared to estimates from human autopsy studies.

3.1.5.4 EPA All Ages Lead Model (AALM)

The AALM simulates blood and tissue Pb masses (μg) and concentrations (μg/g) resulting from exposures to Pb in air, drinking water, surface dust (e.g., indoor dust, soil dust), food, or miscellaneous Pb ingestion pathways. The AALM exposure module allows the user to simulate multi-pathway exposures that are constant or that vary in time increments as small as 1 day and that occur at any age from birth to 90 years. The user can select to run a systemic biokinetics simulation based on either the Leggett (AALM-LG) or O'Flaherty (AALM-OF) biokinetics models. Parameters in both systemic models were re-calibrated with observations of blood, bone, and soft tissue Pb concentrations in children and adults (EPA 2014a). The ICRP Human Respiratory Tract Model (HRTM) deposition and absorption parameters are used in both the AALM-LG and AALM-OF, which allows simulation of inhaled Pb particles of

specified size ranges and absorption kinetics (ICRP 1994). The gastrointestinal tract model includes age-dependent absorption fractions and parameters for RBA of Pb from all ingestion pathways.

The structures of the two systemic biokinetics models in AALM-OF and AALM-LG are based on the O'Flaherty and Leggett models, respectively, with the following modifications. Growth parameters from the O'Flaherty Model are used in both models to simulate age-dependent body weight tissue weights. This provides a means for calculating tissue concentrations as the Pb mass (μg) divided by the tissue weight (g). Concentrations of Pb in bone wet weight are converted to concentration per g bone mineral by dividing the wet weight concentration by the ash fraction of bone. This conversion provides a means for comparing model predictions of bone Pb concentration with bone XRF data, which is typically reported in units of Pb per g bone mineral. Parameters for RBA of Pb in each intake medium include the gastrointestinal tract model. This provides a means for independently adjusting the absorption fraction for each of the intake pathways (including respiratory tract-to-gastrointestinal tract) and maintains mass balance for fecal excretion of unabsorbed Pb. Inhalation, deposition, mucociliary clearance, and absorptive clearance of airborne Pb is simulated with a simplified implementation of the ICRP HRTM.

The AALM systemic biokinetic models were recalibrated from the original Leggett and O'Flaherty Models (EPA 2014b). The sequential recalibration utilized several sources of data on blood and bone Pb concentrations in humans. Parameters that control the uptake and retention of Pb in red blood cells were recalibrated using paired data on whole blood and plasma Pb concentrations in children and adults (Bergdahl et al. 1997c, 1998, 1999; Hernández-Avila et al. 1998; Manton et al. 2001; Schütz et al. 1996; Smith et al. 2002). Parameters that control plasma-to-urine clearance were recalibrated based on clearance estimates from studies that measured paired plasma concentration and urinary Pb excretion in adults (Araki et al. 1986; Chamberlain et al. 1978; Manton and Cook 1984; Manton and Malloy 1983). Autopsy data from children and adults were used to evaluate parameters that control the relationship between of tissue Pb concentrations and bone Pb concentrations (Barry 1975). The relationship between bone and plasma Pb concentrations was evaluated with paired data for plasma Pb concentration and XRF bone Pb in adults (Cake et al. 1996; Hernández-Avila et al. 1998). The long-term rate elimination of Pb from blood and bone was evaluated with data on blood and XRF bone Pb in retired Pb workers (Nilsson et al. 1991).

The calibrated AALM was evaluated with data on PbBs measured in infants (Ryu et al. 1983; Sherlock and Quinn 1986) or adults (Rabinowitz et al. 1976) who consumed known quantities of Pb. In the Ryu et al. (1983) study, PbBs were monitored in formula-fed infants who were fed measured quantiles of

formula. PbBs predicted from the AALM-LG were within 1 SD of the group means and the r^2 for predictions was 0.85. Predictions from the AALM-OF were uniformly higher than observations and the r^2 for predictions was 0.76. Sherlock and Quinn (1986) measured PbB in infants at age 13 weeks and estimated dietary intake of Pb for each infant based on Pb measurements made in duplicate diet samples collected daily during week 13. The observed dose-blood Pb relationship was predicted with r^2 values of 0.95 for AALM-LG and 0.98 for AALM-OF. Rabinowitz et al. (1976) conducted a pharmacokinetics study in which four adults ingested daily doses of [^{207}Pb] nitrate for periods up to 124 days. Concentrations of ^{207}Pb in blood, urine, and feces were then monitored during and following cessation of exposure, and data on daily intakes and blood concentrations for each subject were reported. Absorption fractions for Pb were estimated for each individual based on mass balance in feces. AALM-LG predictions are closer to the observations; r^2 values ranged from 0.92 to 0.98 for four subjects in the study. The AALM-OF predicted a slower accrual and decline of blood Pb, and lower peak PbBs (r^2 <0.25).

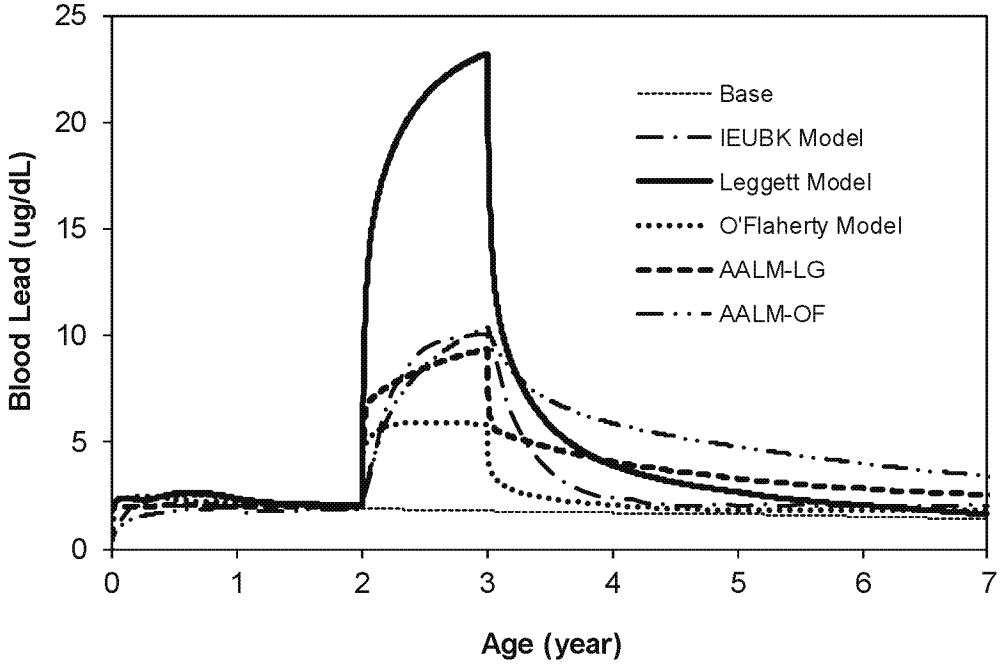
3.1.5.5 Model Comparisons

The O'Flaherty, IEUBK, and Leggett Model differ considerably in the way each represents tissues, exchanges of Pb between tissues, and Pb exposure. The AALM includes biokinetics models based on, but updated from, the O'Flaherty and Leggett models.

Figure 3-4 compares the PbBs predicted by each model for a hypothetical child who ingests 100 μg Pb/day in soil for a period of 1 year beginning at the age of 2 years (e.g., equivalent to ingestion of 100 μg soil/day at a soil Pb concentration of 1,000 mg Pb/g soil). The 100-μg/day exposure is superimposed on a baseline exposure that yields a PbB of approximately 2 μg/dL at 2 years of age. All five models predict an increase in PbB towards a quasi-steady state during the exposure period, followed by a decline towards the pre-exposure baseline PbB with a half-time of approximately 1 month. Predicted PbBs at the end of the 12-month soil exposure period were 10, 23, 5.9, 23, 9.4, and 10.4 μg/dL for the IEUBK Model, Leggett Model, O'Flaherty Model, AALM-LG, and AALM-OF, respectively. Differences in the magnitude of the predicted impact of the soil exposure on PbB reflect differences in assumptions about Pb biokinetics and cannot be attributed solely to different assumptions about Pb bioavailability. Bioavailability assumptions in the models for the age range 2–3 years are: O'Flaherty Model, 45% (50% at age 2 years, decreasing to 40% at age 3 years); IEUBK Model, 30% (soil Pb at low intakes); Leggett Model, 30%; and AALM-LG and AALM-OF 34% (38% at age 2 years and decreasing to 30% at age 3 years). A comparison of model predictions for a similar exposure during adulthood (100 μg Pb/day for 1 year, beginning at age 25) is shown in Figure 3-5. Predicted PbBs at the end of the 12-month soil

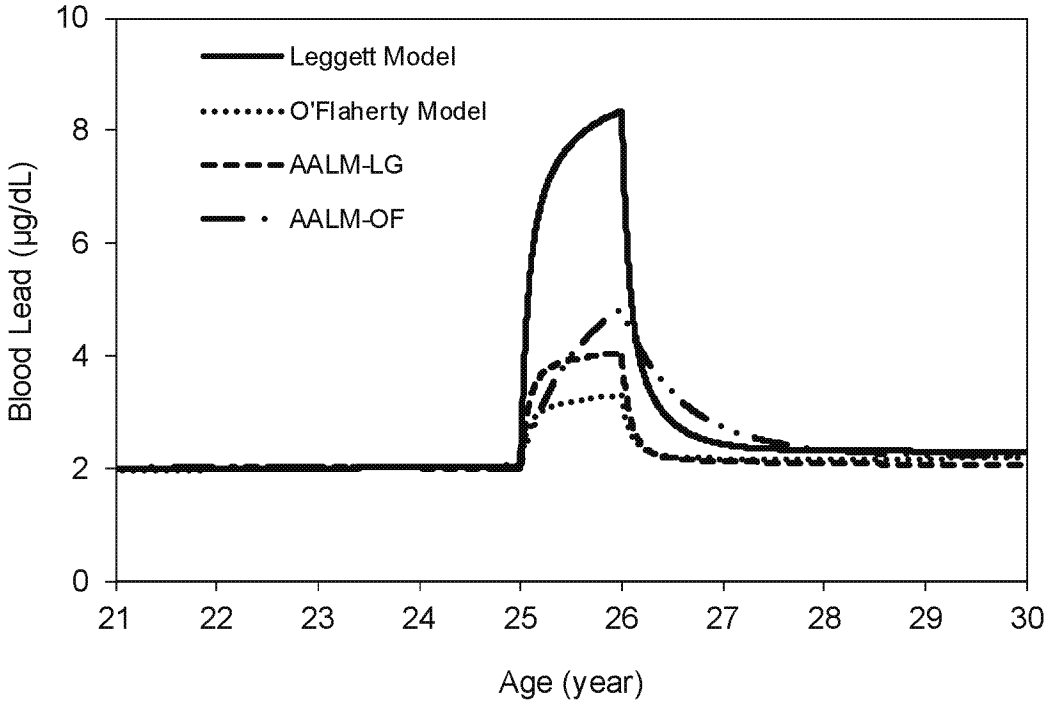
exposure period were 8.4, 3.3, 4.0, and 4.8 µg/dL for the Leggett Model, O'Flaherty Model, AALM-LG, and AALM-OF, respectively. All four models predict a smaller change in PbB in adults, compared to children, for a similar increment in exposure. This is attributed, in part, to assumptions of lower Pb bioavailability in adults (i.e., O'Flaherty, 8%; Leggett, 15%; AALM-LG and AALM-OF, 8%).

Figure 3-4. Blood Lead Concentrations (PbBs) in Children Predicted by the IEUBK, Leggett, and O'Flaherty Models and AALM*



*The simulations are of a hypothetical child who has a PbB of 2 µg/dL at age 2 years, and then experiences a 1-year exposure to 100 µg Pb/day. The 100 µg/day exposure was simulated as an exposure to lead in soil in the IEUBK Model. Default bioavailability assumptions were applied in all three models.

Figure 3-5. Blood Lead Concentrations (PbBs) in Adults Predicted by the Leggett and O'Flaherty Models and AALM*



*The simulations are of a hypothetical adult who has a PbB of 2 µg/dL at age 25 years, and then experiences a 1-year exposure to 100 µg Pb/day. Default bioavailability assumptions were applied in all three models.

3.1.5.6 Slope Factor Models

Slope factor models have been used as simpler alternatives to compartmental models for predicting PbBs, or the change in PbB, associated with a given exposure (Abadin et al. 1997; Bowers et al. 1994; Carlisle and Wade 1992; EPA 2017d; Maddaloni et al. 2005; Stern 1994, 1996). In slope factor models, Pb biokinetics is represented with a simple linear relationship between the PbB and either Pb uptake (biokinetic slope factor, BSF) or Pb intake (intake slope factor, ISF). The models take the general mathematical forms:

$$PbB = E \cdot ISF$$

$$PbB = E \cdot AF \cdot BSF$$

where E is an expression for exposure (e.g., soil intake x soil Pb concentration) and AF is the absorption fraction for Pb in the specific exposure medium of interest. Intake slope factors are based on ingested Pb,

rather than absorbed Pb and, therefore, integrate both absorption and biokinetics into a single slope factor, whereas models that utilize a biokinetic slope factor (BSF) to account for absorption in the relationship include an absorption parameter. Slope factors used in various models are presented in Table 3-2. Of the various models presented in Table 3-2, the Bowers et al. (1994) and EPA (2003b) models implement BSFs. The slope factors used in both models (approximately 0.4 µg/dL per µg Pb/day) are similar to BSFs predicted from the O'Flaherty Model (0.65 µg/dL per µg Pb uptake/day) and Leggett Model (0.43 µg/dL per µg Pb uptake/day) for simulations of adult exposures (Maddaloni et al. 2005).

Table 3-2. Comparison of Slope Factors in Selected Slope Factor Models

Model	Receptor	Intake route	Slope factor		Absorption fraction
			Intake	Biokinetics	
Bowers et al. 1994	Adult	Ingestion of soil/dust	ND	0.375	0.08
Carisle and Wade 1992	Child	Ingestion of soil/dust Ingestion of water	0.07 0.04	ND	ND
Carisle and Wade 1992	Adult	Ingestion of soil/dust Ingestion of water	0.018 0.04	ND	ND
Cal EPA 2017	Child	Ingestion of soil/dust Inhalation of respirable dust Dermal contact	ND 0.192 0.0001	0.16 ND ND	0.44 ND ND
EPA 2017d; Maddaloni et al. 2005	Adult	Ingestion of soil/dust	ND	0.4	0.12
Stern 1994	Child	Ingestion of soil/dust	T (0.056, 0.16, 0.18)	ND	ND
Stern 1996	Adult	Ingestion of soil dust	U (0.014, 0.034)	ND	ND

ND = no data; T = triangular probability distribution function (PDF); U = uniform PDF

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to Pb are discussed in Section 5.7, Populations with Potentially High Exposures.

Age. Children and the elderly are likely to have increased susceptibility to Pb compared to non-elderly adults. As reviewed in Section 3.1.2 (Distribution), Pb crosses the placenta and is distributed to the fetus; neonates are also exposed to Pb in breast milk. Epidemiological studies show that umbilical cord PbB (reflective of neonatal PbB) and PbB in infants are associated with adverse health outcomes during childhood, including decrements in neurological function (reviewed in Chapter 2). Results of a few studies that have followed children to early adulthood show an association between child PbB and behavioral and neuroanatomical changes in adults, suggesting a possible role of exposures in childhood to adult outcomes. Children are likely to be more susceptible than adults to Pb for the following reasons: (1) it is generally accepted that developing systems are more susceptible than mature systems; (2) absorption of Pb is higher in children compared to adults (see Section 3.1.1, Absorption); and (3) children exhibit behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity, pica behavior [the compulsive, habitual consumption of nonfood items]), proximity of breathing zone to entrained surface dust).

Regarding the elderly, it is well-established that physiological functions (e.g., renal, neurological, cardiovascular) decline with age. Thus, populations with age-related compromises in physiological function would be anticipated to be more susceptible to Pb than younger populations. Furthermore, because aging is associated with bone loss, Pb is mobilized into blood, resulting in potential increases in PbB.

Sex. As reviewed in Chapter 2, some epidemiological studies examined health outcomes in populations stratified by sex. However, studies have not demonstrated clear sex-related susceptibilities to Pb-induced toxicity for any health effect outcome. In women, pregnancy, lactation, and post-menopausal status may increase bone demineralization, mobilizing bone Pb into the blood and potentially redistributing Pb to other tissues.

Nutritional Status. As discussed in Sections 3.1 (Toxicokinetics) and 3.4 (Interactions with other Chemicals), dietary calcium and nutritional status of iron and zinc can affect absorption of Pb, potentially leading to alterations in PbB and health effects. See Sections 3.1 and 3.4 for additional details.

Pre-existing Conditions, Diseases, and Exposure to Other Substances. Because health effects associated with Pb are observed in every organ system, it is assumed that any condition or disease that compromises physiological functions could cause increased susceptibility to Pb. Examples of underlying conditions include diseases of the kidney (e.g., glomerular nephritis), neurological system (e.g., autism), hematological system (e.g., anemia, thalassemia), and cardiovascular system (e.g., hypertension, cardiac conduction disorders). Similarly, increased susceptibility to Pb would be anticipated due to use of alcohol, tobacco, or any other substance that causes deficits in physiological function.

Genetic Polymorphisms. Numerous genetic polymorphisms that may alter susceptibility to Pb through altered toxicokinetics (i.e., absorption, distribution, and retention of Pb) or toxicodynamics (e.g., effects) have been identified. The most well-studied polymorphisms are δ-ALAD and the VDR. Several other polymorphisms that may alter susceptibility to Pb have been identified, although little data are available. In addition to the references listed below, information also was obtained from a recent review by Broberg et al. 2015.

ALAD. As reviewed in Section 2.8 (Heath Effects, Hematological), Pb binds to and inhibits δ-ALAD, causing decreased hemoglobin formation, measurable decreases in blood hemoglobin concentration, and anemia. δ-ALAD is the major binding site for Pb in the blood (see Section 3.1.2). As such, polymorphisms of ALAD have the potential to alter Pb toxicokinetics, and thereby alter health effects. Many studies have evaluated the potential effects of ALAD polymorphisms on Pb distribution and toxicity. Information reviewed below was obtained from the following publications: Åkesson et al. (2000); Alexander et al. (1998); Astrin et al. (1987); Battistuzzi et al. (1981); Bellinger et al. (1994); Bergdahl et al. (1997a, 1997b); Chia et al. (2005); Chiu et al. (2013); Fang et al. (2010); Fleming et al. (1998a); Gao et al. (2010); Hsieh et al. (2000); Hu et al. (2001); Huo et al. (2014); Jaffe et al. (2000, 2001); Kim et al. (2004); Krieg et al. (2009); Lee et al. (2001); Ong et al. (1990); Pagliuca et al. (1990); Pawlas et al. (2012); Petrucci et al. (1982); Sakai et al. (2000); Schwartz (1995); Schwartz et al. (1995, 1997a, 1997b, 2000a, 2000b); Scinicariello et al. (2007, 2010); Shen et al. (2001); Sithisarankul et al. (1997); Smith (1995); Suzen et al. (2003); Szymanska-Chaowska et al. (2015); Tasmin et al. (2015); Warrington et al. (2015); Weaver et al. (2008); Wetmur et al. (1991a, 1991b); Wu et al. (2003a); and Zheng et al. (2011).

The ALAD gene encodes for the heme metabolism enzyme δ-ALAD. ALAD is a polymorphic enzyme with two alleles (ALAD-1 and ALAD-2) and three genotypes (ALAD 1,1; ALAD 1,2; and ALAD 2,2). The ALAD 2,2 genotype is rare, and is found in 1% of Caucasians; in contrast, the ALAD 1,1 and ALAD 1,2 genotypes occur in 80 and 19%, respectively, of Caucasians. The ALAD 2,2 genotype occurs in <1% of Asian and African populations. The ALAD-2 protein has a higher binding affinity than the ALAD-1 protein for Pb. Due to this higher binding affinity, it has been proposed that ALAD-2 sequesters Pb in erythrocytes, limiting distribution of Pb to other tissues. Results of epidemiological studies investigating associations between PbB and ALAD and between health effects and carriers of ALAD-2 are not consistent. However, taken together, it appears that ALAD genotype affects the toxicodynamics and toxicokinetics of Pb, but effects remain to be definitively established.

VDR. Several studies have evaluated the potential effects of VDR polymorphisms on Pb uptake and distribution. Information reviewed below was obtained from the following publications: Ames et al. (1999); Cooper and Umbach (1996); Gundacker et al. (2009, 2010); Haynes et al. (2003); Krieg et al. (2010); Morrison et al. (1992); Onalaja and Claudio (2000); Rezende et al. (2008); Schwartz et al. (2000a, 2000b); Szymanska-Chaowska et al. (2015); Theppeang et al. (2004); and Weaver et al. (2003b).

The VDR is located in the nucleus of intestinal, renal, and bone cells. It is involved in maintaining calcium and phosphate homeostasis and regulating bone metabolism. Binding of vitamin D3 (the active form of vitamin D) to the VDR activates genes that encode for various calcium-binding proteins involved in intestinal absorption and accumulation of calcium in bone. The VDR regulates the production of calcium-binding proteins, and accounts for up to 75% of the total genetic effect on bone density. Because Pb can replace and mimic calcium, the VDR plays a critical role in the accumulation of Pb in bone. The VDR has several polymorphic forms that are defined based on restriction enzyme digestion; these include FokI with three genotypes (FF, Ff, and ff) and BsmI with three genotypes (BB, Bb, bb). The FF genotype has been associated with higher PbB and increased bone mineral density and calcium uptake. The BB genotype has been associated with higher PbB and bone Pb. However, the role of VDR polymorphisms in the Pb uptake into bone remains to be fully elucidated.

Hemochromatosis gene (HFE). Information on HFE polymorphisms was taken from the following publications: Åkesson et al. (2000); Barton et al. (1994); Fan et al. (2014); Hopkins et al. (2008); Onalaja and Claudio (2000); Park et al. (2009a); Wang et al. (2007); Wright et al. (2004); and Zhang et al. (2010).

Hemochromatosis is an autosomal, recessive disease characterized by the excessive accumulation of iron in the body. In individuals with hemochromatosis, excess iron accumulates in various organs of the body and causes damage to the liver and compromises cardiovascular function. Hemochromatosis is caused by mutations of the HFE gene, which result in defects to the HFE protein. In individuals with normal HFE, HFE binds to transferrin, decreasing the gastrointestinal absorption of iron; however, in individuals with hemochromatosis, the HFE protein is not functional, leading to an increased accumulation of iron. The absorption of Pb is linked to iron status such that Pb absorption increases when iron is limited. HFE polymorphisms have been shown to enhance Pb-induced cognitive impairment (Wang et al. 2007) and the HFE H63D polymorphism appears to enhance positive associations between bone Pb and pulse pressure (Zhang et al. 2010). However, the influence of HFE variants on absorption and health effects of Pb is still being defined.

Other polymorphisms. Several other polymorphisms have been examined to evaluate potential alterations in susceptibility to adverse effects of Pb; however, little data are available. These include:

- *Apoprotein E (APOE).* APOE is an intracellular transporter of cholesterol and fatty acids that is synthesized by astrocytes in the brain and plays a key role in the structure of cell membranes and myelin. There are three alleles of the APOE gene: E2, E3, and E4. It has been proposed that APOE gene variants may alter susceptibility to Pb-induced changes in neurodevelopment and neurological deficits (Stewart et al. 2002; Wright et al. 2003a).
- *Dopamine receptor D4 (DRD4), Dopamine Receptor D2 (DRD2), and Dopamine Transporter (DAT1).* Pb is associated with alterations in the dopaminergic system, which is involved in cognition and behavior. Thus, polymorphisms of DRD4, DRD2, and DAT1 may alter susceptibility to Pb-induced neurocognitive impairment (Froehlich et al. 2007; Kordas et al. 2011; Roy et al. 2011).
- *Glutathione S-transferase mu 1 (GSTM1).* Glutathione is an intracellular scavenger of oxidants and electrophiles. It is encoded by the polymorphic gene GSTM1. Genetic alterations causing a decrease in functional glutathione could result in increased oxidative damage or inflammation (Kim et al. 2007).
- *Endothelial nitric oxide synthase (eNOS).* Nitric oxide, an endogenous signaling molecule involved in vasodilation, is produced by a family of nitric oxide synthase enzymes, including eNOS. Polymorphisms of eNOS could increase susceptibility to Pb (Barbosa et al. 2006b).
- *Metallothionein (MT).* MT binds to and sequesters Pb. It has been proposed that polymorphisms of MT (MT1 and MT2) may affect binding of Pb to MT and lead to an increased PbB (Chen et al. 2010; Fernandes et al. 2016; Yang et al. 2013b).

- *Peptide transporter 2 (PEPT2)*. Polymorphisms of PEPT2 have been associated with increased PbB in children (Sobin et al. 2009).
- *Tumor necrosis factor-alpha (TNF-α)*: TNF-α is a cell signaling protein involved in the development of inflammation. Genetic variants in TNF-α have the potential to alter susceptibility to Pb (Kim et al. 2007).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to Pb are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for Pb from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by Pb are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Biomarkers of exposure in practical use today are measurements of total Pb levels in body fluids or tissues, such as blood, bone, or urine. Tetraalkyl Pb compounds may also be measured in the breath. Of these, PbB is the most widely used and is considered to be the most reliable biomarker for general clinical use and public health surveillance. Currently, PbB measurement is the screening test of choice to identify children with elevated PbBs (CDC 2012d). Venous sampling of blood is preferable to finger prick sampling, which has a considerable risk of surface Pb contamination from the finger if proper finger cleaning is not carried out. In children, PbBs greater than the blood lead reference values (BLRV) identify high-risk childhood populations and geographic areas most in need of primary prevention (CDC 2012d). In 2012, the BLRV was defined as >5 µg/dL (CDC 2012d).

PbB. Measurement of PbB is the most widely used biomarker of Pb exposure. Elevated PbB (e.g., >5 µg/dL) is an indication of excessive exposure in infants and children (CDC 2012d). The biological exposure index (BEI) for Pb in blood of exposed workers is 30 µg/dL (ACGIH 2001). The Occupational Safety and Health Administration's (OSHA) permissible exposure limit (PEL) for lead (50 µg/m^3 air, 8-hour time-weighted average [TWA]) was established to keep a majority of worker PbBs below 40 µg/dL (OSHA 2016a). The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for workers (50 µg/m^3 air, 8-hour TWA) is established to ensure that the PbB does not exceed 60 µg/dL (NIOSH 2016b).

The extensive use of PbB as a dose metric reflects mainly the greater feasibility of incorporating PbB measurements into clinical or epidemiological studies, compared to other potential dose indicators, such as Pb in kidney, plasma, or bone. PbB measurements have several limitations as measures of total Pb body burden. Blood comprises <2% of the total Pb burden; most of the Pb burden resides in bone (Barry 1975). Pb is eliminated from blood more rapidly than from bone (Behinaein et al. 2014; Brito et al. 2005; Chamberlain et al. 1978; Griffin et al. 1975; Manton et al. 2001; Nie et al. 2005; Nilsson et al. 1991; Rabinowitz et al. 1976; Rentschler et al. 2012); therefore, the Pb concentration in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (Graziano 1994; Lyngbye et al. 1990b). Slow release of Pb from bone can contribute to blood Pb levels long after external exposure has ceased (Fleming et al.

1997; Inskip et al. 1996; Kehoe 1987; McNeill et al. 2000; O'Flaherty et al. 1982; Smith et al. 1996). The relationship between Pb intake and PbB is curvilinear; the increment in PbB per unit of intake decreases with increasing PbB (Ryu et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1982, 1984). Pb intake-PbB relationships also vary with age as a result of age-dependency of gastrointestinal absorption of Pb, and vary with diet and nutritional status (Mushak 1991). A practical outcome of the above characteristics of PbB is that PbB can change relatively rapidly (e.g., weeks) in response to changes in exposure; thus, PbB can be influenced by short-term variability in exposure that may have only minor effects on total Pb body burden. A single PbB determination cannot distinguish between lower-level intermediate or chronic exposure and higher-level acute exposure. Similarly, a single measurement may fail to detect a higher exposure that occurred (or ended) several months earlier. Time-integrated measurements of PbB (CBLI) may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Armstrong et al. 1992; Behinaein et al. 2014; Chuang et al. 2000; Fleming et al. 1997; Gerhardsson et al. 1993; Healey et al. 2008; Hu et al. 2007; McNeill et al. 2000; Nie et al. 2011a; Roels et al. 1995). The correlation observed between CBLI and tibia bone Pb concentrations provides supporting evidence for this (Hu et al. 2007).

Bone and Tooth Pb Measurements. The development of noninvasive XRF techniques for measuring Pb concentrations in bone has enabled the exploration of bone Pb as a biomarker of Pb exposure in children and in adults (Behinaein et al. 2011; Chettle et al. 2003; Hu et al. 2007; Ji et al. 2014; Nie et al. 2011b; Specht et al. 2016; Todd et al. 2000). Pb in bone is considered a biomarker of cumulative exposure to Pb because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Pb is not distributed uniformly in bone. Pb will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in both cortical and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect Pb in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna primarily reflect primarily Pb in cortical bone. Pb levels in cortical bone may be a better indicator of long-term cumulative exposure than Pb in trabecular bone, possibly because Pb in trabecular bone may exchange more actively with Pb in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of Pb in cortical bone, compared to trabecular bone (Behinaein et al. 2014; Borjesson et al. 1997; Brito et al. 2005; Nie et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal studies that have repeatedly measured bone Pb (by XRF) over many years have shown more rapid declines in trabecular bone

compared to cortical bone (Kim et al. 1997; Wilker et al. 2011). Estimates of cortical bone Pb elimination half-times (5–50 years) show a dependence on Pb burden, with longer half-times in people who have higher total body burdens (estimated from CBLI) and bone Pb burdens (Behinaein et al. 2014; Brito et al. 2005; Nie et al. 2005). Further evidence that cortical bone Pb measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone Pb measurements have been compared to PbB. Pb levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of Pb in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone Pb measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary PbB measurements (Behinaein et al. 2012; Borjesson et al. 1997; Hu et al. 2007; Roels et al. 1994). Bone Pb levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone Pb may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Standard methods for bone Pb XRF measurements have not been universally accepted, in part, because the technology continues to be improved, and this needs to be considered in comparisons of measurements reported by different laboratories and at different times in development of the methodology used. Historically, two XRF methods have seen the most use in bone Pb epidemiology: K-shell and L-shell methods. The K-shell method is the more widely used, although, improvements in L-shell technology continue to be reported (Nie et al. 2011a). One study reported a correlation of 0.65 between bone Pb measurements made with a portable L-shell device and a K-shell method (Nie et al. 2011a). In general, recent advances in K-shell technology have yielded higher sensitivities (approximately 3 μg/g tibia mineral; Behinaein et al. 2011) than L-shell technology (approximately 8 μg/g tibia bone mineral; Nie et al. 2011a). Precision of K-shell XRF bone Pb measurements have been extensively discussed (Aro et al. 2000; Behinaein et al. 2014; Todd et al. 2000, 2001, 2002). Methodological factors can contribute substantially to observed variability in bone Pb measurements in populations (Behinaein et al. 2014). These factors include bone Pb target, radioactive source, measurement time, and data reduction methods (e.g., approach to handling negative values). Measurement uncertainty also appears to contribute by biological factors, such as BMI and bone mineral content (Behinaein et al. 2014; Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008). The association between BMI and measurement uncertainty may reflect the effect attenuation of the XRF signal by tissue overlaying the target bone site (Behinaein et al. 2014). Bone mineral can be a factor because XRF measures bone Pb fluorescence in relation to fluorescence from bone calcium and the result is expressed in units of μg Pb per g bone mineral. As a

result, variability in bone mineral content can contribute to variability in measured bone Pb. Typically, potential associations between bone density and bone Pb concentration are not evaluated in epidemiologic studies (Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008). An important consequence of expressing bone Pb measures relative to bone mineral content is that lower bone mineral density is associated with greater measurement uncertainty in bone Pb. This uncertainty can have important implications for studies in older women for whom low bone mineral density is more common than in other populations including men and younger adults.

Tooth Pb has been considered a potential biomarker for measuring long-term exposure to Pb (e.g., years) because Pb that accumulates in tooth dentin and enamel appears to be retained until the tooth is shed or extracted (Costa de Almeida et al. 2007; Ericson 2001; Fosse et al. 1995; Gomes et al. 2004; Gulson and Wilson 1994: Gulson et al. 1996; Omar et al. 2001; Rabinowitz 1995; Rabinowitz et al. 1989, 1993; Robbins et al. 2010; Steenhout and Pourtois 1987; Tvinnereim et al. 1997). Formation of enamel and primary dentin of deciduous teeth begins *in utero* and is complete prior to the time children begin to crawl. Formation of secondary dentin begins after completion of the tooth root and continues through childhood until the tooth is lost, or otherwise loses vitality. Pb in shed deciduous teeth is not uniformly distributed. Differences in Pb levels and stable isotope signatures of the enamel and dentin suggest that Pb uptake occurs differentially in enamel and dentin (Gulson 1996; Gulson and Wilson 1994). Pb in enamel is thought to reflect primarily Pb exposure that occurs *in utero* and early infancy, prior to tooth eruption. Dentin appears to continue to accumulate Pb after eruption of the tooth; therefore, dentin Pb is thought to reflect exposure that occurs up to the time the teeth are shed or extracted (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). The technique of laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) allows measurement of Pb levels in regions of dentin formed at various times during deciduous tooth formation *in utero* and after birth (Arora et al. 2014; Shepherd et al. 2016). Accumulation of Pb in dentin of permanent teeth may continue for the life of the tooth (Steenhout 1982; Steenhout and Pourtois 1981). Because enamel is in direct contact with the external environment, enamel Pb levels may be more influenced than dentin Pb by external Pb levels and tooth wear (Purchase and Fergusson 1986).

An analysis of eight cross-sectional and/or prospective studies that reported tooth Pb and PbBs of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth Pb levels ranged from <3 to >12 μg/g. Dentin Pb was found to be predictive of Pb in tibia, patella, and mean bone Pb in 32 of 63 subjects at follow-up of ≤13 years (Kim et al. 1996b). The authors estimated that a 10 μg/g increase in dentin Pb levels in childhood was predictive of a 1 μg/g increase in tibia Pb levels, a

5 μg/g in patella Pb levels, and a 3 μg/g increase in mean bone Pb among the young adults. Arora et al. (2014) found that Pb levels in primary (prenatal) dentin were more strongly correlated with PbBs at birth (correlation coefficient, r=0.69, n=27), whereas Pb levels in secondary (postnatal) dentin were more strongly correlated with CBLI (r=0.38, n=75). Shepherd et al. (2016) combined LA-ICP-MS with histological determinations of dentin age to reconstruct the history of incorporation of environmental Pb from various sources.

Plasma Pb Concentration. The concentration of Pb in plasma is extremely difficult to measure accurately because levels in plasma are near the quantitation limits of most analytical techniques (e.g., approximately 0.04 μg/dL at PbB of 10 μg/dL) (Bergdahl and Skerfving 1997; Bergdahl et al. 1997a) and because hemolysis that occurs with typical analytical practices can contribute to substantial measurement error (Bergdahl et al. 1998, 2006; Cavalleri et al. 1978; Smith et al. 1998a). ICP-MS offers sensitivity sufficient for measurements of Pb in plasma (Schütz et al. 1996). The technique has been applied to assessing Pb exposures in adults (Barbosa et al. 2006a; Cake et al. 1996; Hernandez-Avila et al. 1998; Manton et al. 2001; Smith et al. 2002; Tellez-Rojo et al. 2004; Tian et al. 2013). A direct comparison of Pb concentrations in plasma and serum yielded similar results (Bergdahl et al. 2006); however, the interchangeability of plasma and serum Pb measurements for biomonitoring of Pb exposure or body burden had not been thoroughly evaluated in large numbers of subjects (Bergdahl et al. 2006; Manton et al. 2001; Smith et al. 2002).

Urinary Pb. Measurements of urinary Pb levels have been used to assess Pb exposure (e.g., Chiang et al. 2008; Fels et al. 1998; Fukui et al. 1999; Gerhardsson et al. 1992; Lilis et al. 1968; Lin et al. 2001; Mendy et al. 2012; Mortada et al. 2001; Navas-Acien et al. 2005; Rentschler et al. 2012; Roels et al. 1994; Sun et al. 2008b). However, like PbB, urinary Pb excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing Pb body burden or long-term exposure (Sakai 2000; Skerfving 1988). Although collection of urine is noninvasive, urine Pb levels exhibit variability with PbB, and interpretation of urine Pb levels requires estimates of GFR and measurement of urine volume (NTP 2012). A significant, but relatively weak correlation between urinary Pb levels (μg/dg creatinine) and individual Pb intakes (μg/day) was observed in a study of 10–12-year-old children (β: 0.053, R=0.320, p=0.02, N=57; Chiang et al. 2008). In this study, urine sampling and measurements used to estimate intake were separated by as long as 6 months for some children, which may have contributed to the relatively weak correlation. The measurement is further complicated by variability in urine volume, which can affect concentrations independent of excretion rate (Diamond 1988) and the potential effects of decrements in kidney function on excretion, in association with high, nephrotoxic Pb exposures or kidney

disease (Lilis et al. 1968; Wedeen et al. 1975). Urinary Pb concentration increases exponentially with PbB and can exhibit relatively high intra-individual variability, even at similar PbBs (Gulson et al. 1998a; Skerfving et al. 1985). However, the relationship between plasma Pb and urinary Pb (μg Pb/g creatinine) was linear in a small group of children (Rentschler et al. 2012). The linear relationship between plasma and urinary Pb may reflect the importance of plasma Pb in determining the rate of glomerular filtration and renal tubular transport of Pb (see Section 3.1.4). Urinary diethyl Pb has been proposed as a qualitative marker of exposure to tetraethyl Pb (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

The measurement of Pb excreted in urine following an injection (intravenous or intramuscular) of the chelating agent, calcium disodium EDTA (*EDTA provocation*), or oral dosing with dimercaptosuccinic acid (DMSA) has been used to detect elevated body burden of Pb in adults (Biagini et al. 1977; Lee et al. 2009; Lilis et al. 1968; Lin et al. 2003, 2006a, 2006b; Schwartz et al. 2000a, 2000c; Wedeen 1992; Wedeen et al. 1975)and children (Chisolm et al. 1976; Markowitz and Rosen 1981). However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning." The assay is not a substitute for PbB measurements in the clinical setting. Note that children whose PbBs are ≥45 μg/dL should not receive a provocative chelation test; they should be immediately referred for appropriate chelation therapy (CDC 2002a, 2012f). For additional information on recommended actions based on PbB level in children and adults, see Section 3.5 (Methods for Reducing Toxic Effects). Further limitations for routine use of the test are that EDTA must be given parenterally and requires timed urine collections. A study conducted in rats found that intraperitoneal administration of a single dose of EDTA following 3–4-month exposures to Pb in drinking water increased levels of Pb in the liver and brain (Cory-Slechta et al. 1987) raising concern for similar effects in humans who undergo the EDTA provocation test. The use of EDTA to assess bone stores of Pb (Wedeen 1992) is largely being supplanted by more direct, noninvasive procedures for measuring Pb in bone. DMSA is a Pb chelating agent that can be administered orally. DMSA-chelatable Pb has been used as marker of Pb body burden in adults (Schwartz et al. 1997, 2000a, 2000c; Scinicariello et al. 2007; Weaver et al. 2003a, 2003b).

Pb in Saliva and Sweat. Pb is excreted in human saliva and sweat (Genuis et al. 2011; Lilley et al. 1988; Omokhodion and Crockford 1991; Rabinowitz et al. 1976; Stauber and Florence 1988; Sears et al. 2012; Stauber et al. 1994). Sweat has not been widely adopted for monitoring Pb exposures. Lilley et al.

(1988) found that Pb concentrations in sweat were elevated in Pb workers; however, sweat and PbBs were poorly correlated. This may reflect excretion of Pb in or on the skin that had not been absorbed into blood. Studies conducted in rats have found relatively strong correlations between Pb concentrations in plasma and saliva (e.g., $r^2>0.9$), compared to blood Pb and saliva; therefore, saliva may serve as a better predictor of plasma Pb than PbB (Timchalk et al. 2006). However, studies of saliva Pb conducted in humans have had mixed results, with some studies showing relatively strong correlations between salivary Pb concentration and PbB (Brodeur et al. 1983; Omokhodion and Crockford 1991; P'an 1981), and other studies showing weak or inconsistent relationships (Barbosa et al. 2006c; Costa de Almeida et al. 2009, 2010, 2011; Nriagu et al. 2006). Variable outcomes from these studies may reflect differences in PbBs, exposure history and/or dental health (i.e., transfer of Pb between dentin and saliva), and methods used for determining Pb in saliva. Other confounding factors reported in the literature include uncontrolled variation in salivary flow rates (Barbosa et al. 2005; Esteban and Castano 2009) and potential blood contamination of saliva (Koh and Koh 2007).

Hair and Nail Pb. Pb is incorporated into human hair and hair roots (Bos et al. 1985; Rabinowitz et al. 1976) and has been explored as a possibly noninvasive approach for estimating Pb body burden (Gerhardsson et al. 1995b; Wilhelm et al. 1989). The method is subject to error from contamination of the surface with environmental Pb and contaminants in artificial hair treatments (i.e., dyeing, bleaching, permanents) and is a relatively poor predictor of PbB, particularly at low concentrations (<12 μg/dL) (Campbell and Toribara 2001; Drasch et al. 1997; Esteban et al. 1999; Rodrigues et al. 2008). Nevertheless, levels of Pb in hair were positively correlated with children's classroom attention deficit behavior in a study (Tuthill 1996). Pb in hair was correlated with liver and kidney Pb in a study of deceased smelter workers (Gerhardsson et al. 1995b). Correlations between maternal and infant hair Pb concentrations have been observed (Kordas et al. 2010). Although hair Pb measurements have been used in some epidemiologic studies (Bao et al. 2009; Huel et al. 2008; Marcus et al. 2010; Shah et al. 2011), an empirical basis for interpreting hair Pb measurements in terms of body burden or exposure has not been firmly established. Nail Pb has also been utilized as a marker of Pb exposure, although nails may be contaminated with Pb from external sources (Barbosa et al. 2005; Gerhardsson et al. 1995b).

Semen Pb. Pb concentrations in semen have been explored as an internal exposure biomarker for adverse effects of Pb on the testes (Hernandez-Ochoa et al. 2005; Kasperczyk et al. 2015; Slivkova et al. 2009; Taha et al. 2013; Wu et al. 2012). Correlations between concentrations of Pb in semen and blood have been reported and vary in strength across studies (Alexander et al. 1998a, 1998b; Farias et al. 2005; Hernandez-Ochoa et al. 2005; Mendiola et al. 2011; Telisman et al. 2000). This variation may relate, in

part, to analytical challenges in the measurement of the relatively low concentrations of Pb in semen. Using ICP-MS and rigorous collection methods to avoid contamination, Farias et al. (2005) reported a detection limit of 0.2 μg/L semen. Mean semen Pb concentration in a group of 160 men (age range 19–48 years) who were not exposed to Pb occupationally was 2.66 μg/L (range 0.08–19.42) and was significantly correlated with PbB (mean 10.8 μg/dL, range 4.5–40.2) and tibia bone Pb (mean 14.51 μg/g, range not-detected–44.71 μg/g).

Stable Pb Isotopes. Analysis of the relative abundance of stable isotopes of Pb in blood and other accessible body fluids (e.g., breast milk, urine) has been used to differentiate exposures from multiple sources (Flegal and Smith 1995). Relative abundances of stable isotopes of Pb (^{204}Pb, ^{206}Pb, ^{207}Pb, and ^{208}Pb) in Pb ores vary with the age of the ore (which determines the extent to which the parent isotopes have undergone radioactive decay to stable Pb). Humans have Pb isotope abundance profiles that reflect the profiles of Pb deposits to which they have been exposed. Pb isotope studies can be used to identify sources of Pb contributing to exposure. Similarly, if exposure abruptly changes to a Pb source having a different isotope abundance profile, the kinetics of the change in profile in the person can be measured, reflecting the kinetics of uptake and distribution of Pb from the new source (Gulson et al. 2003; Maddaloni et al. 1998; Manton et al. 2003). Numerous examples of the application of stable isotope abundance measurements for studying sources of Pb exposures have been reported (Angle et al. 1995; Graziano et al. 1996; Gulson and Wilson 1994; Gulson et al. 1996, 1997b, 1999c, 2016; Manton 1977, 1998).

Effect Biomarkers Used to Assess Exposure to Pb. Certain physiological changes that are associated with Pb exposure have been used as biomarkers of exposure (see Section 3.3.2). These include measurements of biomarkers of impaired heme biosynthesis (blood zinc protoporphyrin, urinary coproporphyrin, erythrocyte ALAD activity, serum ALA). These types of measurements have largely been supplanted with measurement of PbB for the purpose of assessing Pb exposure due to the higher sensitivity of PbB measurements in quantifying lower level Pb exposures.

3.3.2 Biomarkers of Effect

Certain effects of Pb have been used in diagnosing Pb poisoning to support measurements of PbB; however, none of these diagnostic aids are considered preferable to measurement of PbB. A multisite study of populations living near four NPL sites was conducted to assess the relationship between exposure (PbB and area of residence) and biomarkers of four organ systems: immune system

dysfunction, kidney dysfunction, liver dysfunction, and hematopoietic dysfunction (ATSDR 1995). The geometric mean PbB in those living in the target areas was 4.26 μg/dL (n=1,645) compared with 3.45 μg/dL for a group living in comparison areas (n=493). In children <6 years old, the corresponding means were 5.37 versus 3.96 μg/dL. In subjects ≥15 years old, the target and comparison values were 3.06 and 3.63 μg/dL, respectively. Ninety percent of target and 93% of comparison area participants had PbBs <10 μg/dL. Pb in soil and water was found to be higher in comparison areas than in the target areas, but Pb in house dust and in interior paint was higher in the target areas. PbB correlated with Pb in soil and dust, but not with Pb in paint and water. Multivariate regression analyses showed that of all the biomarkers analyzed, PbB was significantly associated with, and predictive of, hematocrit in adults ≥15 years of age and with increased mean serum IgA in children 6–71 months of age. The biological significance of these associations is unclear since both hematocrit and IgA levels were well within normal ranges and were hardly different than levels in subjects from the comparison areas.

Pb inhibits heme biosynthesis, which is necessary for production of red blood cells. Hematologic tests such as hemoglobin concentration may suggest toxicity, but this is not specific for Pb (Bernard and Becker 1988). However, inhibition of ferrochelatase in the heme pathway causes accumulation of protoporphyrin in erythrocytes (CDC 1985). Most protoporphyrin in erythrocytes (about 90%) exists as zinc-protoporphyrin (ZPP). This fraction is preferentially measured by hematofluorometers. Extraction methods measure all of the protoporphyrin present, but strip the zinc from the ZPP during the extraction process. For this reason, extraction results are sometimes referred to as (zinc) free erythrocyte protoporphyrin (FEP). Although the chemical forms measured by the two methods differ slightly, on a weight basis, they are roughly equivalent; thus, results reported as EP, ZPP, or FEP all reflect essentially the same analyte. An elevated EP level is one of the earliest and most reliable indicators of impairment of heme biosynthesis and reflects average Pb levels at the site of erythropoiesis over the previous 4 months (Janin et al. 1985). The concentration of EP rises above background at PbBs of 25–30 μg/dL, above which, there is a positive correlation between PbB and EP (CDC 1985; Gennart et al. 1992a; Roels and Lauwerys 1987; Soldin et al. 2003; Wildt et al. 1987). Pb toxicity is generally considered to be present when a PbB ≥10 μg/dL is associated with an EP level ≥35 μg/dL (CDC 1991; Somashekaraiah et al. 1990). This effect is detectable in circulating erythrocytes only after a lag time reflecting maturation in which the entire population of red blood cells has turned over (i.e., 120 days) (EPA 1986a; Moore and Goldberg 1985). Similarly, elevated EP can reflect iron deficiency, sickle cell anemia, and hyperbilirubinemia (jaundice). Therefore, reliance on EP levels alone for initial screening could result in an appreciable number of false positive cases (CDC 1985; Mahaffey and Annest 1986; Marcus and Schwartz 1987). Conversely, since EP does not go up until the PbB exceeds 25 μg/dL, and the level of

concern is 5 µg/dL, relying on EP measures would result in many false negative cases. Some have estimated that relying only on ZPP screening to predict future Pb toxicity would miss approximately three cases with toxic PbBs in every 200 workers at risk (Froom et al. 1998). A limitation of measuring porphyrin accumulation is that porphyrin is labile because of photochemical decomposition; thus, assay samples must be protected from light. However, other diseases or conditions such as porphyria, liver cirrhosis, iron deficiency, age, and alcoholism may also produce similar effects on heme synthesis (Somashekaraiah et al. 1990).

ALAD, an enzyme occurring early in the heme pathway, is also considered a sensitive indicator of Pb effect (Graziano 1994; Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). ALAD activity is negatively correlated with PbBs of 5–95 µg/dL, with >50% inhibition occurring at PbBs >20 µg/dL (Hernberg et al. 1970; Morita et al. 1997; Roels and Lauwerys 1987). However, ALAD activity may also be decreased with other diseases or conditions such as porphyria, liver cirrhosis, and alcoholism (Somashekaraiah et al. 1990). ALAD was found to be a more sensitive biomarker than urinary ALA and ZPP at PbBs between 21 and 30 µg/dL (Schuhmacher et al. 1997). A marked increase in urinary excretion of ALA, the intermediate that accumulates from decreased ALAD, can be detected when PbB exceeds 35 µg/dL in adults and 25–75 µg/dL in children (NAS 1972b; Roels and Lauwerys 1987; Sakai and Morita 1996; Schuhmacher et al. 1997).

Another potential biomarker for hematologic effects of Pb is the observation of basophilic stippling and premature erythrocyte hemolysis (Paglia et al. 1975, 1977). Pb can impair the activity of pyrimidine 5'-nucleotidase, resulting in a corresponding increase in pyrimidine nucleotides in red blood cells, which leads to a deficiency in maturing erythroid elements and thus, decreased red blood cells. However, this effect is nonspecific; it is encountered with benzene and arsenic poisoning (Smith et al. 1938) and in a genetically-induced enzyme-deficiency syndrome (Paglia et al. 1975, 1977). Furthermore, since basophilic stippling is not universally found in chronic Pb poisoning, it is relatively insensitive to lesser degrees of Pb toxicity (CDC 1985). The activity of adenine dinucleotide synthetase (NADS) in erythrocytes has also been explored as a biomarker for predicting PbBs >40 µg/dL; NADS activity is negatively correlated with PbB over the range 5–80 µg/dL (Morita et al. 1997).

Reduction in the serum 1,25-dihydroxyvitamin D concentration has been reported as an indicator of increased Pb absorption or Pb concentrations in the blood (Rosen et al. 1980). Pb inhibits the formation of this active metabolite of vitamin D, which occurs in bone mineral metabolism (EPA 1986a; Landrigan 1989). Children with PbBs of 12–120 µg/dL showed decreased serum 1,25-dihydroxyvitamin D

concentrations comparable to those found in patients with hypoparathyroidism, uremia, and metabolic bone disease (Mahaffey et al. 1982; Rosen et al. 1980). This biomarker is clearly not specific for Pb exposure and several diseases can influence this measurement.

One of the most sensitive systems affected by Pb exposure is the nervous system. Encephalopathy is characterized by symptoms such as coma, seizures, ataxia, apathy, bizarre behavior, and incoordination (CDC 1985). Children are more sensitive to neurological changes than adults. In children, encephalopathy has been associated with PbBs as low as 70 μg/dL (CDC 1985). An early sign of peripheral manifestations of neurotoxicity is gastrointestinal colic, which can occur with PbBs above 50 μg/dL. The most sensitive peripheral index of neurotoxicity of Pb is reported to be slowed conduction velocity in small motor fibers of the ulnar nerve in workers with PbBs of 30–40 μg/dL (Landrigan 1989). Other potential biomarkers of Pb suggested for neurotoxicity in workers are neurological and behavioral tests, as well as cognitive and visual sensory function tests (Williamson and Teo 1986). However, these tests are not specific to elevated Pb exposure.

Functional deficits associated with Pb-induced nephrotoxicity increase in severity with increasing PbB. Effects include decreased glomerular filtration, enzymuria and proteinuria, and impaired transport function. Biomarkers for these changes include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, β2μ-globulin, α1μ-globulin, retinol binding protein). However, none of these markers are specific for Pb-induced nephrotoxicity. A characteristic histologic feature of Pb nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Interactions between Pb and other chemicals can be classified into two categories: interactions with contaminants that are commonly found together with Pb at hazardous waste sites, and interactions with essential elements (ATSDR 2004a, 2004b, 2006; EPA 2014c).

Interactions with Other Contaminants. Several metals and metalloids frequently are found together with Pb at hazardous waste sites, including arsenic (As), cadmium (Cd), manganese (Mn), zinc (Zn), copper (Cu), and inorganic mercury (Hg). ATSDR (2004a, 2004b, 2006) has conducted assessments to predict interactions of these chemicals with Pb; conclusions are presented in Table 3-3. For each co-contaminant, interactions were classified as less than additive (indicating an antagonistic effect with Pb), additive

(indicating no effect of combined exposure), or greater than additive (indicating a synergistic effect with Pb). Greater-than-additive effects were observed for neurological effects for As and Cd, male reproductive effects for Cd, and renal effects for Hg. Interactions for other metals were either less than additive or additive for cardiovascular (Cd, Zn), developmental (Zn), hematological (As, Cd, Mn, Zn, Cu), immunological (Cd), neurological effects (Zn), renal (As, Cd, Mn, Zn, Cu), and male reproductive (Zn) effects. Other metals that may interact with Pb include selenium and chromium(VI) (Nordberg et al. 2015). Observed interactions of metals and metalloids with Pb could be the results of alterations to Pb toxicokinetics, toxicodynamics, or a combination of both.

Table 3-3. Influence of Other Metals and Metalloids on Lead (Pb) Toxicity

	Metal					
Organ system	Arsenic[a]	Cadmium[a]	Manganese[b]	Zinc[b]	Copper[b]	Inorganic mercury[c]
Cardiovascular	–	< or 0	–	<	–	–
Developmental	–	–	–	<	–	–
Hematological	< or 0	< or 0	0	< or 0	<	–
Immunological	–	<	–	–	–	–
Neurological	>	>	–	< or 0	<	–
Renal	0	< or 0	0	<	–	>
Male reproductive	–	>	–	<	–	–

[a]ATSDR 2004a.
[b]ATSDR 2004b.
[c]ATSDR 2006.

< = less than additive; 0 = additive (no effect); > = greater than additive; – = not assessed

Interactions with Essential Elements. In physiological systems, Pb mimics divalent cations (calcium, iron, zinc). Substitution of Pb for essential elements in membrane transport systems is the mechanism by which Pb is absorbed from the intestine and crosses cell membranes throughout the body. Thus, numerous interactions between Pb and essential elements have been observed, including the following (additional details on these finding are provided in Section 3.1, Toxicokinetics):

- Dietary calcium intake appears to affect Pb absorption. An inverse relationship has been observed between dietary calcium intake and PbBs in children (Elias et al. 2007; Mahaffey et al. 1986; Schell et al. 2004; Ziegler et al. 1978).
- Nutritional iron status may affect Pb absorption in children. Higher PbBs have been observed in iron-deficient children compared to children who are iron replete. This observation suggests that

iron deficiency may result in higher absorption of Pb or, possibly, other changes in Pb biokinetics that would contribute to higher PbBs (Mahaffey and Annest 1986; Marcus and Schwartz 1987).

- In young children (ages 6–12 months), PbB increased in association with lower dietary Zn levels (Schell et al. 2004). It is not clear, however, if these associations were caused by changes in Pb absorption.

3.5 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to lead. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to lead. When specific exposures have occurred, poison control centers, medical toxicologists, or other clinicians with expertise and experience treating and managing lead exposed adults and/or children should be consulted. The following resources provide specific information about treatment and management of patients following exposure to lead:

AAP. 2005. Lead exposure in children: Prevention, detection, and management. Pediatrics 116(4):1036-1046. 10.1542/peds.2005-1947.

AAP. 2016. Council on Environmental Health. Prevention of childhood lead toxicity. Pediatrics 38(1):e20161493

ATSDR. 2017. Case studies in environmental medicine (CSEM). Lead toxicity. https://www.atsdr.cdc.gov/csem/lead/docs/csem-lead_toxicity_508.pdf. August 30, 2018.

Calello DP, Henretig FM. 2014. Lead. In: Goldfrank's toxicologic emergencies. Tenth ed. New York, NY: McGraw-Hill, 1219-1234.

Holland MG, Cawthon D. 2016. ACOEM Position Statement. Workplace lead exposure. J Occup Environ Med 58(12):e371-e374.

Leikin JB, Paloucek FP. 2008. Lead. In: Poisoning and toxicology handbook. Fourth ed. Boca Raton, FL: CRC Press, 807-811.

CDC. 2002a. Managing elevated blood levels among young children. Recommendations from the Advisory Committee on Childhood Lead Poisoning. Centers for Disease Control and Prevention. https://www.cdc.gov/nceh/lead/casemanagement/managingEBLLs.pdf. July 18, 2018.

Kosnett MJ. 2001. Lead. In: Ford M, Delaney KA, Ling L, et al., eds. Clinical toxicology. St. Louis: WB Saunders, 723-736.

Kosnett MJ. 2005. Lead. In: Brent J, Wallace KL, Burkhart KK, et al., eds. Critical care toxicology. Philadelphia, PA: Elsevier Mosby, 821-836.

PEHSU. 2013. Recommendations on medical management of childhood lead exposure and poisoning. Pediatric Environmental Health Specialty Units.

Additional publicly available clinical resources for the health care professional can be found in Appendix D.

3.5.1 Reducing Absorption Following Exposure

No treatment modalities to reduce lead absorption have been developed. Therefore, the most important intervention is to identify and remove the source of exposure (AAP 2005, 2016; ATSDR 2017; CDC 2012f). Lead absorption from the gastrointestinal tract is influenced by nutrition, especially calcium, iron, and vitamin C (AAP 2005; CDC 2012f). It is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of lead and that children eat regular meals since more lead is absorbed on an empty stomach (AAP 2005; CDC 2002a, 2012f). Good sources of iron include liver, fortified cereal, cooked legumes, and spinach, whereas milk, yogurt, cheese, and cooked greens are good sources of calcium (CDC 1991).

General recommendations to reduce absorption of lead following acute exposure include the following (AAP 2016; ATSDR 2017; Calello and Henretig 2014; Kosnett et al. 2007):

- remove the individual from the source of exposure;
- mitigate source of exposure;
- if suspected that elevated PbB is due to ingestion of a foreign object (e.g., Pb paint chips, toys or jewelry containing Pb, Pb ammunition), radiographic imaging is suggested;
- if elevated PbB is due to ingestion of a foreign object, decontamination of the bowel (surgical or gastric lavage) is indicated; and
- ensure that diet is adequate in calcium, iron, and vitamin C.

For children, specific recommended actions based on PbB levels are summarized in Table 3-4. The current CDC reference level PbB is 5 µg/dL. This value is based on the 97.5th percentile of the PbB distribution among children 1–5 years of age in the United States, using data generated by NHANES (CDC 2012d). Recent NHANES surveys show that the Pb reference level continues to decline (CDC 2018a).

Table 3-4. Recommended Actions Based on Child Blood Lead Level (PbB)

PbB (µg/dL)	Recommended actions
Reference level[a]	• Education on environmental sources of Pb and sufficient dietary nutrition • Follow-up PbB monitoring

Reference level and ≤45	• Follow recommendations for <Reference value
	• Complete history and physical examination
	• Laboratory analysis
	  ○ Monitor iron status
	  ○ Consider measurement of hemoglobin or hematocrit
	• Neurodevelopmental monitoring
	• Abdominal radiography and bowel decontamination if ingestion of Pb particulate is suspected
	• Conduct environmental investigation and Pb hazard reduction

≥45 and ≤69	• Follow recommendations for ≥Reference level and ≤45
	• Laboratory analyses
	  ○ Hemoglobin or hematocrit
	  ○ Iron status
	  ○ Zinc protoporphyrin
	• Oral chelation therapy
	• Consider hospitalization if cannot assure mitigation of Pb source

≥70	• Hospitalize • Initiate chelation therapy with consultation with a medical toxicologist or pediatric environmental health expert or unit • Follow recommendations for ≥45 and ≤69

[a]5 µg/dL (CDC 2012d).

Source: CDC 2012f

For occupational exposures, OSHA and NIOSH have developed recommendations to reduce Pb exposure through procedures and surveillance. In 1987, NIOSH developed the Adult Blood Lead Epidemiology and Surveillance (ABLES) program, which was created to reduce the rate of adults with PbB ≥10 µg/dL through coordinated efforts of several federal and state agencies (NIOSH 2017). In 2015, NIOSH designated PbB of 5 µg/dL as the PbB reference level and defined elevated PbB as PbB ≥5 µg/dL (NIOSH 2017). The OSHA (1995) mandated rule on lead provides recommendations to reduce occupational Pb exposure for general industry, shipyard employment, and construction through use of respirators, protective clothing, routine biological monitoring of PbB and zinc protoporphyrin, and medical assessments for workers with elevated PbB. More recently, Holland and Cawthon (2016) suggested the actions based on PbB levels, with a baseline PbB <5 µg/dL (Table 3-5).

Table 3-5. Recommended Actions for Workers Based on Pb Level (PbB)

PbB (µg/dL)	Recommended actions
All workers	• PbB goal is <5 µg/dL • PbB monitoring at initial employment • Monitor every 2 months for the first 6 months of employment or change of work task • <5 µg/dL for pregnant workers
≥5–9	• Increase monitoring • Pregnant workers or workers who are trying to become pregnant should be medically removed from work; return to work may be considered if two consecutive PbB measurements are <5 µg/dL
10–19	• Monitor PbB every 2 months • Evaluate exposure, controls, and work practices • Mandatory removal for pregnant workers; return to work may be considered if two consecutive PbB measurements are <5 µg/dL
≥20	• Repeat PbB measurement in 4 weeks; if PbB remains ≥20 µg/dL, remove from exposure • Monthly PbB measurement; return to work after two consecutive monthly PbB measurements are <15 µg/dL • Evaluate exposure, controls, and work practices • Continue PbB monitoring as noted above
≥30	• Removed from work • Monthly PbB measurement; return to work after two consecutive monthly PbB measurements are <15 µg/dL • Evaluate exposure, controls, and work practices • Continue PbB monitoring as noted above

[a]Source: Holland and Cawthon (2016)

3.5.2 Reducing Body Burden

Lead is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94 and 73% of the total body burden of lead is found in bones, respectively. Lead may be stored in bone for long periods of time, but may be mobilized, thus achieving a steady state of intercompartmental distribution (see Section 3.3.2).

Currently available methods to obviate the toxic effects of lead are based on their ability to reduce the body burden of lead by chelation. All of the chelating agents bind inorganic lead, enhance its excretion, and facilitate the transfer of lead from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated lead via the kidney, caution should be used when treating a patient with renal failure. For all cases where chelation therapy is considered or implemented, medical providers should consult with a medical toxicologist or an expert in the medical management of lead toxicity (CDC 2002a, 2012f). Chelation treatment should be administered in

conjunction with meticulous supportive therapy (Calello and Henretig 2014). Most of the information below regarding chelators was obtained from Calello and Henretig (2014) and Kosnett (2005, 2007).

Several pharmacological substances are available for chelation therapy for Pb intoxication. Chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL), $CaNa_2$-EDTA (or EDTA), and 2,3-dimercaptosuccinic acid (DMSA; Succimer®). Dosages and administration protocols for these agents vary with patient age, PbB level, and symptom types and severity. Specific treatment protocols should be developed in consultation with clinical experts in the management of lead toxicity for the most current chelation therapy procedures for children and adults (CDC 2002a, 2012f).

Dimercaprol (BAL). The mechanism of action of BAL is through formation of stable chelate-metal compounds intra- and extracellularly. BAL is administered parenterally. The onset of action for BAL is 30 minutes. BAL increases fecal excretion of lead as chelated lead is excreted predominantly in bile within 4–6 hours; BAL also increases urinary excretion of chelated lead. A number of adverse reactions have been associated with BAL, including nausea, vomiting, hypertension, tachycardia, headache, increased secretions, anxiety, abdominal pain, and fever.

$CaNa_2$-EDTA (or EDTA). EDTA works by forming a stable metal-chelate complex that is excreted by the kidney. It increases renal excretion of lead 20–50 times. EDTA is administered parenterally. Numerous adverse effects have been described due to treatment with EDTA including rash, fever, fatigue, thirst, myalgias, chills, and cardiac dysrhythmias. Since EDTA chelates zinc, patients with low zinc stores may be adversely affected by EDTA. Since EDTA also chelates other metals, administration of EDTA (or BAL) to persons occupationally exposed to cadmium may result in increased renal excretion of cadmium and renal damage.

2,3-Dimercaptosuccinic acid (DMSA; Succimer®). The mechanism of action of DMSA is similar to BAL. DMSA is administered orally. DMSA has been shown to be as effective as EDTA in increasing the urinary excretion of lead. Minimal adverse effects that have been reported include anorexia, nausea, vomiting, and rashes. DMSA increases the excretion of zinc, but to a much lesser extent than other chelators, and has minimal effects on calcium, iron, magnesium, and copper.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Pb is a naturally occurring element with an abundance of 0.0016% in the earth's crust (Davidson et al. 2014). It is a member of Group 14 (IVA) of the periodic table. Natural Pb is a mixture of four stable isotopes: ^{204}Pb (1.4%), ^{206}Pb (24.1%), ^{207}Pb (22.1%), and ^{208}Pb (52.4%). The Pb isotopes ^{206}Pb, ^{207}Pb, and ^{208}Pb are the stable decay product of the naturally occurring decay series of uranium, actinium, and thorium, respectively (Haynes 2014).

Pb is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world (King et al. 2014). Its properties, such as corrosion resistance, density, and low melting point, make it a familiar metal in pipes, solder, weights, and storage batteries. The chemical identities of Pb and several of its compounds are provided in Table 4-1.

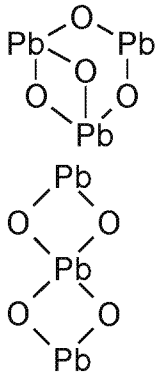
Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead	Lead(II) acetate	Lead(II) azide	Lead(II) bromide
Synonym(s) and registered trade name(s)	C.I. 77575; C.I. Pigment metal 4; Glover; Lead flake; Lead S2; Omaha; Omaha & Grant; SI; SO[a]	Acetic acid lead(2+) salt (2:1); neutral lead acetate; plumbous acetate; normal lead acetate; sugar of lead; salt of Saturn[b]	Lead azide[b]	Lead bromide ($PbBr_2$); plumbous bromide[b]
Chemical formula	Pb[b]	$Pb(CH_3CO_2)_2$[b]	$Pb(N_3)_2$[b]	$PbBr_2$[b]
Chemical structure	Not applicable	Not applicable	Not applicable	Not applicable
CAS Registry Number	7439-92-1[b]	301-04-2[b]	13424-46-9[b]	10031-22-8[b]

Table 4-1. Chemical Identity of Lead and Compounds

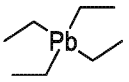
Characteristic	Lead(II) chloride	Lead(II) chromate	Lead(II) tetrafluoroborate[c]	Lead(II) iodide
Synonym(s) and registered trade name(s)	Lead chloride ($PbCl_2$); Lead(2+) chloride; Plumbous chloride[b]	Chromic acid (H_2CrO_4 lead(2+) salt (1:1); Chrome yellow; Cologne yellow; King's yellow; Leipzig yellow; Paris yellow; C.I. Pigment Yellow 34; lead chromium oxide ($PbCrO_4$); plumbous chromate; C.I. 77600[b]	Tetrafluoro borate(1-) Lead(2+)[a]	Lead iodide (PbI_2); Plumbous iodide[b]
Chemical formula	$PbCl_2$[b]	$PbCrO_4$[b]	$Pb(BF_4)_2$[a]	PbI_2[b]
Chemical structure	Not applicable	Not applicable	Not applicable	Not applicable
CAS Registry Number	7758-95-4[b]	7758-97-6[b]	13814-96-5[a]	10101-63-0[b]

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead molybdenum chromate	Lead(II) nitrate	Lead(II) oxide	Lead(II,II,IV) oxide
Synonym(s) and registered trade name(s)	Chromic acid, lead and molybdenum salt; chromic acid lead salt with lead molybdate; C.I. Pigment Red 104; Lead chromate, Molybdenum-Lead chromate; Molybdenum Orange[a]	Nitric acid lead(2+) salt (2:1); Plumbous nitrate[b]	C.I. 77577; C.I. Pigment Yellow 46; Lead oxide; Lead oxide yellow; Lead protoxide; Litharge; Litharge Yellow L-28; Massicot; Massicotite; Plumbous oxide; Yellow lead ocher[a]	Lead tetraoxide; Lead tetroxide; Lead oxide red; C.I. Pigment Red 105; C.I. 77578; Gold satinobre; Lead orthoplumbate; Lead oxide (3:4); Mineral Orange; Mineral Red; Paris Red; Saturn Red; Minium; Plumboplumbic oxide; Red Lead; Red Lead oxide; Trilead tetraoxide[d,e]
Chemical formula	No data	$Pb(NO_3)_2$[b]	PbO[a]	Pb_3O_4[e]
Chemical structure	Not applicable	Not applicable	Not applicable	
CAS Registry Number	12709-98-7[a]	10099-74-8[b]	1317-36-8[a]	1314-41-6[d]

Characteristic	Lead(II) phosphate	Lead(II) styphnate	Lead(II) sulfate
Synonym(s) and registered trade name(s)	C.I. 77622; Lead orthophosphate; Lead phosphate (3:2); Lead(2+) phosphate; normal lead orthophosphate; Phosphoric acid, lead(2+) salt (2:3); Plumbous phosphate; Trilead phosphate[a]	Lead trinitroresorcinate[f]	Anglesite; C.I. 77630; C.I. Pigment White 3; Fast White; Freemans White Lead; Lead bottoms; Milk white; Mulhouse White; Sulfuric acid, lead(2+) salt (1:1)[a]
Chemical formula	$Pb_3(PO_4)_2$[a]	$Pb(C_6HN_3O_8)_2$[f]	$PbSO_4$[b]
Chemical structure	Not applicable	Not applicable	Not applicable
CAS Registry Number	7446-27-7[a]	15245-44-0[f]	7446-14-2[b]

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead(II) sulfide	Tetraethyl lead	Lead(II) carbonate
Synonym(s) and registered trade name(s)	C.I. 77640; Galena; Natural lead sulfide; Plumbous sulfide[a]	Tetraethylplumbane; Lead tetraethyl; TEL[b]	Carbonic acid, lead(2+) salt (1:1); Cerussite; Dibasic lead carbonate; Lead(2+) carbonate; White lead[a]
Chemical formula	PbS[a]	$Pb(C_2H_5)_4$[a]	$PbCO_3$[a]
Chemical structure	Not applicable		Not applicable
CAS Registry Number	1314-87-0[a]	78-00-2[b]	598-63-0[a]

[a]Lewis 2012.
[b]O'Neil et al. 2015 2013.
[c]Stable only in aqueous solution (Haynes 2014).
[d]CHEMIDplus 2018.
[e]Haynes 2014.
[f]Boileau et al. 2012.

CAS = Chemical Abstracts Services

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Pb, a blueish-white metal with bright luster, is very soft, highly malleable, ductile, a poor conductor of electricity, and is very resistant to corrosion (Haynes 2014). A clean lead surface will not be attacked by dry air; however, in moist air, the surface will react and become coated with a layer of lead(II) oxide (PbO). This coating may be hydrated and combine with carbon dioxide to form lead(II) carbonate ($PbCO_3$) (Carr et al. 2004). This protective coating of insoluble Pb compounds slows or halts corrosion of the underlying metal. Pb is rarely found in its metallic form in nature and commonly occurs as a mineral with sulfur or oxygen. The most important lead mineral is galena (PbS). Other common Pb-containing minerals include anglesite ($PbSO_4$), cerussite ($PbCO_3$), and minium (Pb_3O_4) (Carr et al. 2004; Davidson et al. 2014; Haynes 2014).

Pb can exist in the 0 oxidation state in metallic Pb and in compounds as the +2 or +4 oxidation states. In the environment, Pb is primarily found in the +2 state in inorganic compounds. The chemistry of inorganic Pb compounds is generally similar to that of the Group 2(II) or alkaline earth metals. There are three common oxides of Pb: lead(II) oxide (PbO); lead(II,IV) oxide or lead tetroxide (Pb_3O_4); and lead(IV) oxide or lead dioxide (PbO_2). The +4 state is only formed under strongly oxidizing conditions. Inorganic Pb(+4) compounds are relatively unstable and would not be expected to be found under

ordinary environmental conditions. Pb is amphoteric, meaning that it can react with acids and bases. In acid, Pb forms Pb(+2) (plumbous) and Pb(+4) (plumbic) salts and in basic solution, it forms plumbites (PbO_2^{2-}) and plumbates ($Pb(OH)_6^{2-}$) (Carr et al. 2004). In organolead compounds, Pb is typically in the tetravalent (+4) oxidation state (Carr et al. 2004; Haynes 2014).

Data on the physical and chemical properties of lead and several of its compounds are provided in Table 4-2.

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead	Lead(II) acetate	Lead(II) azide	Lead(II) bromide
Molecular weight	207.2[a]	325.3[b]	291.24[a]	367.0[b]
Color	Bluish-white, silvery, gray metal[a]	White crystals[b]	Needles or white powder[a]	White orthorhombic crystals[b]
Physical state	Solid	Solid	Solid	Solid
Melting point	327.4°C[a]	280°C[b]	Decomposes at 190°C[c]	371°C[b]
Boiling point	1,740°C[a]	Decomposes[b]	No data	892°C[b]
Density	11.34 g/cm^3 at 20°C[a]	3.25 g/cm^3[b]	4.17 g/cm^3 at 20°C[c]	6.69 g/cm^3[b]
Odor	No data	Slightly acetic odor (trihydrate)[a]	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble[d]	443,000 mg/L at 20°C[b]	230 mg/L at 18°C[a]	9,750 mg/L at 25°C[b]
Acids	Soluble in dilute nitric acid[d]; reacts with sulfuric acid[a]	Soluble in acid[e]	Freely soluble in acetic acid[a]	No data
Bases	No data	Soluble in alkali[e]	No data	No data
Organic solvents	Soluble in glycerin; slightly soluble in alcohol[e]	Slightly soluble in alcohol; freely soluble in glycerol[d]	No data	Insoluble in alcohol[b]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1.77 mmHg at 1,000°C[a]	No data	No data	0.0075 mmHg at 374°C[b]
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[f]	Not relevant[f]	Not relevant[f]	Not relevant[f]
Explosive limits	No data	No data	Explodes at 350°C[a]	No data
Valence state	0	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) chloride	Lead(II) chromate	Lead(II) tetrafluoroborate	Lead iodide
Molecular weight	278.1[g]	323.19[a]	380.8[b]	461.05[g]
Color	White, orthorhombic needles[g]	Yellow or orange-yellow powder[a]	No data	Yellow hexagonal crystals[g]
Physical state	Solid	Solid	Stable only in aqueous solution[b]	Solid
Melting point	501°C[g]	844°C[a]	No data	402°C[g]
Boiling point	950°C[g]	No data	No data	954°C[g]
Density	5.85 g/cm^3[g]	6.12 g/cm^3[b]	No data	6.16 g/cm^3[g]
Odor	No data	No data	No data	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	9,900 mg/L at 20°C[g]	0.2 mg/L[a]	Soluble[b]	630 mg/L at 20°C[g]
Acids	Slightly soluble in dilute hydrochloric acid[g]	Soluble in dilute nitric acid; insoluble in acetic acid[a]	No data	No data
Bases	Slightly soluble in dilute ammonia[g]	No data	No data	No data
Organic solvents	Insoluble in alcohol[g]	No data	No data	Insoluble in alcohol[g]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	7.5 mmHg at 637°C[b]	No data	No data	0.75 mmHg at 470°C[b]
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[f]	Not relevant[f]	Not relevant[f]	Not relevant[f]
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead molybdenum chromate	Lead(II) nitrate	Lead(II) oxide	Lead(II,II,IV) oxide
Molecular weight	No data	331.23[g]	223.21[g]	685.57[e]
Color	No data	Cubic or monoclinic colorless crystals[g]	Reddish-yellow; yellow (above 489°C)[g]	Bright red heavy powder[a]; red tetrahedral crystals[b]
Physical state	No data	Solid	Solid	Solid
Melting point	No data	Begins to decompose above 205°C[g]	897°C (begins to sublime before melting)[g]	830°C[b]; 500°C[e]
Boiling point	No data	No data	Decomposes at 1,472°C[g]	Decomposes between 500-530°C[d]
Density	No data	4.53 g/cm^3[g]	9.53 g/cm^3 (Litharge)[g]; 9.6 g/cm^3 (Massicot)[g]	8.92 g/cm^3[b]; 9.1 g/cm^3[e]
Odor	No data	No data	No data	No data
Odor threshold:	No data	No data	No data	No data
Solubility:				
Water	No data	56:5 g/100 mL at 20°C[g]	50.4 mg/L at 25°C (Litharge)[g]; 106.5 mg/L at 25°C (Massicot)[g]	Insoluble in water[d]
Acid	No data	Insoluble in concentrated nitric acid[a]	Soluble[g]	Dissolves in acetic acid or hot hydrochloric acid[b,g]
Base	No data	Soluble in alkali and ammonia[g]	Soluble[g]	No data
Organic solvents	No data	87.7 mg/L (43% aqueous ethanol) at 22°C[g]	Insoluble in alcohol[a]	Insoluble in alcohol[g]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	0.0075 mmHg at 724°C[b]	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[f]	Not relevant[f]	Not relevant[f]	Not relevant[f]
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2, +2, +4

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) phosphate	Lead(II) styphnate	Lead(II) sulfate
Molecular weight	811.54[a]	450.29[h]	303.25[g]
Color	White powder[a]	Monoclinic orange-yellow crystal (monohydrate)[b]	White, heavy, crystalline powder[a]
Physical state	Solid	Solid	Solid
Melting point	1,014°C[a]	No data	1,170°C[g]
Boiling point	No data	No data	No data
Density	6.9 g/cm^3[a]	3.1 g/cm^3 (monohydrate); 2.9 g/cm^3 (anhydrous)[b]	6.2 g/cm^3[g]
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water	Insoluble[b]	Insoluble[b]	42.5 mg/L at 25°C[g]
Acid	Soluble in nitric acid[a]	No data	Soluble in concentrated acids[g]
Base	Soluble in fixed alkali hydroxides[a]	No data	Soluble in alkalies[g]
Organic solvents	Insoluble in alcohol[a]	No data	Insoluble in alcohol[a]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	Not relevant[f]	Not relevant[f]	Not relevant[f]
Explosive limits	No data	Detonates at 260°C[b]	No data
Valence state	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) sulfide	Tetraethyl lead	Lead(II) carbonate
Molecular weight	239.25[g]	323.45[a]	267.22[g]
Color	Metallic black cubic crystals[g]	Colorless[a]	Colorless rhombic crystals[g]
Physical state	Solid	Liquid[a]	Solid
Melting point	1,114°C[d]	No data	315°C (decomposes)[g]
Boiling point	Sublimes at 1,281°C[d]	200 °C; 227.7°C (with decomposition)[a]	No data
Density	7.57–7.59 g/cm^3[g]	1.653 g/cm^3[a]	6.6 g/cm^3[g]
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water	124.4 mg/L 20°C[g]	0.29 mg/L[i]	1.1 mg/L at 20°C[g]
Acid	Soluble in nitric acid[g]	No data	Soluble[g]
Base	Insoluble in alkalies[d]	No data	Soluble in alkalies; insoluble in ammonia[g]
Organic solvents	Insoluble in alcohol[a]	Soluble in benzene, petroleum ether, gasoline; slightly soluble in alcohol[a]	Insoluble in alcohol[g]
Partition coefficients:			
Log K_{ow}	No data	4.15[j]	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	0.0075 mmHg at 705°C[b]	0.26 mmHg at 25°C[j]	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	200°F (93°C) (closed cup)[k]	No data
Flammability limits	No data	Lower flammable limit: 1.8% by volume[k]	No data
Conversion factors	Not relevant[f]	No data	Not relevant[f]
Explosive limits	No data	No data	No data
Valence state	+2	+4	+2

[a]O'Neil et al. 2013.
[b]Haynes 2014.
[c]Akvavan 2004.
[d]Larrañaga et al. 2016.
[e]Jacob 2012.
[f]Since these compounds exist in the atmosphere in the particulate state, their concentrations are expressed as µg/m^3 only.
[g]Carr et al. 2004.
[h]Molecular weight calculated from atomic weights.
[i]Feldhake and Stevens 1963.
[j]Wang et al. 1996.
[k]NFPA 2002.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Pb and Pb compounds have been identified in at least 1,274 and 47 sites, respectively, of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites evaluated for Pb is not known. The number of sites in each state is shown in Figures Figure 5-1 and Figure 5-2, respectively. Of these 1,274 sites for Pb, 1,261 are located within the United States, 2 are located in the Virgin Islands, 2 are located in Guam, and 9 are located in Puerto Rico (not shown). All the sites for Pb compounds are only in the United States.

Figure 5-1. Number of NPL Sites with Lead Contamination

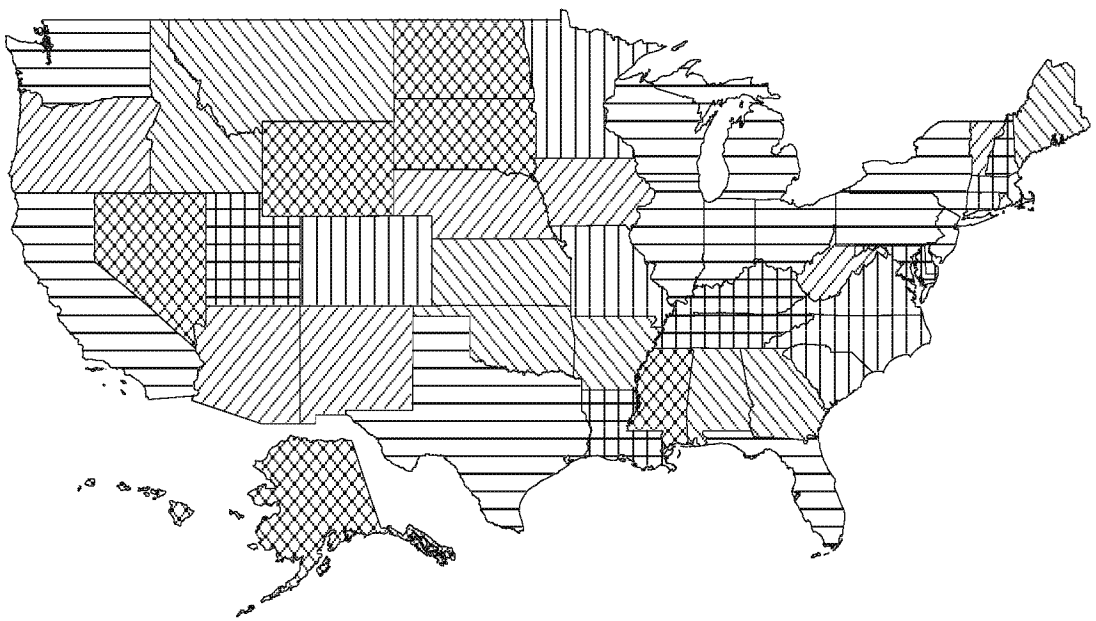
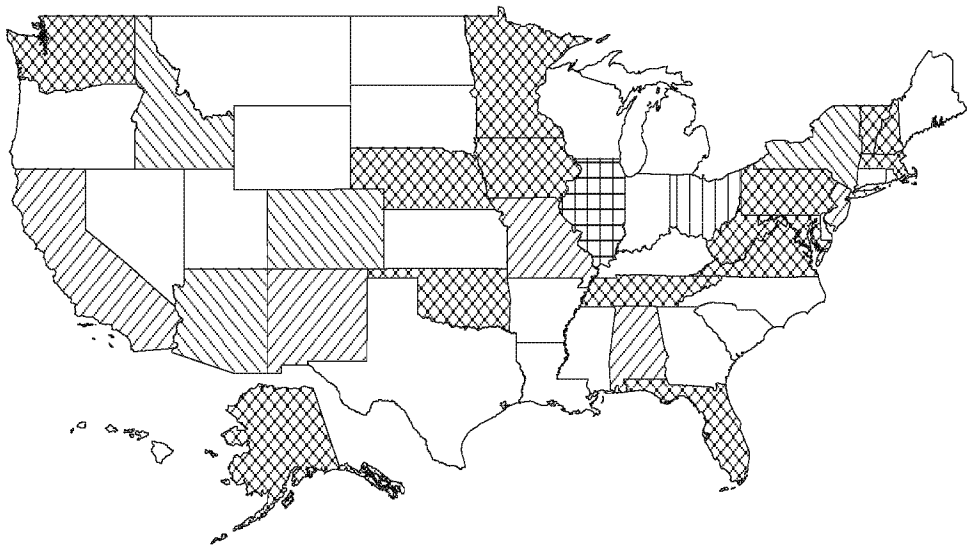


Figure 5-2. Number of NPL Sites with Lead Compound Contamination



- Pb is an element found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world.
- The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. For adults, exposure to levels of Pb beyond background are usually associated with occupational exposures.
- For children, exposure to high levels of Pb are associated with living in areas contaminated by Pb (e.g., soil or indoor dust in older homes with Pb paint). Exposure usually occurs by hand-to-mouth activities.
- As an element, Pb does not degrade. However, particulate matter contaminated with Pb can move through air, water, and soil.
- Atmospheric deposition is the largest source of Pb found in soils. Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb.
- Pb adsorbs strongly to most soils, which limits the rate of leaching of Pb from soil. Soil acidity (pH) is the most important factor affecting solubility, mobility, and phytoavailability of Pb in soil.